Archives of Dermatology and Syphilology

VOLUME 45 MARCH 1942 NUMBER 3

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SEROLOGIC DIAGNOSIS OF SYPHILIS

VALUE OF COMPLEMENT FIXATION AND AGGLUTINATION WITH SPIROCHETAL ANTIGENS AND RELATION OF SPIROCHETAL ANTIBODY TO THE WASSERMANN REAGIN

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PHILADELPHIA

When complement fixation in syphilis was discovered by Wassermann and his colleagues and independently by Detre in 1906, it was naturally assumed to be a specific reaction between the syphilis antibody and Spirochaeta pallida present in the extracts of syphilitic tissues employed as antigens. On the subsequent discovery that saline and alcoholic extracts of normal mammalian tissues served equally well as antigen in the test, the idea of the Wassermann reaction being a specific antigen-antibody reaction was largely abandoned with the suggestion that the reaction was biologically nonspecific owing to the production in syphilis of a reagin characterized by its ability to sensitize and flocculate tissue lipids in vitro with the fixation of complement.

But on the successful cultivation of S. pallida in pure culture by Noguchi in 1911 it was possible for the first time to investigate the problem by the use of saline suspensions and alcoholic extracts of the cultivated spirochetes as antigens. The results of these early investigations [1] showed that spirochetal antigens gave complement fixation in syphilis but that in general terms they were inferior in sensitivity to alcoholic extracts of heart reenforced with cholesterol. However, these investigations indicated that either a true antibody was produced in

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1. (*a*) Noguchi, H.: Experimental Research in Syphilis with Special Reference to Spirochaeta Pallida (Treponema Pallidum), J. A. M. A. **58**:1163 (April 20) 1912. (*b*) Craig, C. F., and Nichols, H. J.: A Study of Complement Fixation in Syphilis with Spirochaeta Culture Antigens, J. Exper. Med. **16**:336, 1912. (*c*) Kolmer, J. A.; Williams, W. W., and Laubaugh, E. E.: A Study of Complement Fixation in Syphilis with Treponema Antigens, J. M. Research **28**:345, 1913. (*d*) Kolmer, J. A., and Broadwell, S.: The Relation of the Luetin Skin Reaction to Immunity in Syphilis (Including the Treponemacidal Action of Human Serum in Syphilis), J. Immunol. **1**:429, 1916.

syphilis reacting specifically with spirochetes in addition to the reagin reacting with tissue lipids in the Wassermann and flocculation reactions or that the reactions occurring with spirochetal antigens were due to the fixation of complement by the reagin and the lipids of the spirochetes.[1c]

As a result, the idea of possible specific complement fixation in syphilis by specific antibody and antigens of S. pallida was never completely abandoned in the following years,[2] and in 1929 Gaehtgens and Otto [3] greatly renewed interest in the subject by stating that a phenolized saline suspension of the Reiter strain of S. pallida as antigen yielded specific complement fixation reactions in syphilis which were probably separate and independent of the Wassermann and flocculation reactions as well as more sensitive than the latter, especially in treated syphilis.

Since then such a large number of reports have appeared, especially in the German literature (summarized in tables 2 and 4), that I thought it advisable and helpful to review and discuss the present status of the sensitivity, specificity and practical value of spirochetal antigens in the serologic diagnosis of syphilis and also the question whether there occurs in syphilitic serum a specific antibody for S. pallida separate and apart from the reagin reacting with alcoholic extracts of heart, as suggested by Gaehtgens [4] and Beck,[5] or whether the Wassermann and flocculation reactions on the one hand and complement fixation with spirochetal antigens on the other are due to spirochetal antibodies, as claimed by Eagle and Hogan.[6]

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2. (*a*) Schereschewsky, J.: Syphilisimmunitätsversuche mit Spirochätenreinkulturen, Deutsche med. Wchnschr. **39**:1676, 1913. (*b*) Hinkleman, A. J.: Treponema Pallida Antigens in the Wassermann Reaction, Am. J. Syph. **9**: 181, 1925. (*c*) Hecht, H.: Vergleichende Untersuchungen mit dem Spirochätenextrakt (Klopstock), Ztschr. f. Immunitätforsch. u. exper. Therap. **54**: 365, 1928. (*d*) Klopstock, F.: Die Entstehung der syphilitischen Blutveränderung und die Eigenschaften eines Spirochätenimmunserums, Deutsche med. Wchnschr. **52**:1460, 1926; Experimentelle Untersuchungen zur Entstehung der syphilitischen Blutveränderung, Klin. Wchnschr. **6**:685, 1927. (*e*) Höltzer, R. R., and Popoff, W. J.: Versuche über Herstellung des syphilitischen Antigens aus Pallidakulturen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **59**:501, 1928.

3. (*a*) Gaehtgens, W., and Otto, A.: Ueber die Brauchbarkeit eines wässerigen carbolisierten Pallidaantigen für die serologische Syphilisdiagnose, Med. Klin. **25**:873, 1929. (*b*) Gaehtgens, W.: Theoretisches und Praktisches über die Wirkung eines karbolisierten wässerigen Pallidaantigens, Ztschr. f. Immunitätsforsch u. exper. Therap. **63**:398, 1929.

4. Gaehtgens, W.: Concerning a Carbolized Watery Pallida Antigen for the Serological Diagnosis of Syphilis, Urol. & Cutan. Rev. **34**:165, 1930.

5. Beck, A.: The Role of the Spirochaete in the Wassermann Reaction, J. Hyg. **39**:298, 1939.

6. Eagle, H., and Hogan, R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes: Their Relation to So-Called Wassermann Reagin, and Their Significance for the Serodiagnosis of Syphilis, J. Exper. Med. **71**:215, 1940.

SENSITIVITY OF ANTIGENS OF CULTIVATED S. PALLIDA

A. *With Human Syphilitic Serums.*—As shown in table 1, the sensitivity of antigens prepared of pure cultures of six strains of alleged S. pallida in complement fixation tests employing human syphilitic serums has varied from 21.2 to 100 per cent. However, sensitivity is probably better expressed by the results reported within the last two years,[7] showing 72 to 100 per cent positive reactions with spirochetal antigens, as compared with 64.2 to 100 per cent positive Wassermann reactions.

TABLE 1.—*Complement Fixation by Antigens of Cultivated S. Pallida and Syphilitic and Nonsyphilitic Human Serums*

	Spirochetal Antigens		Syphilitic Serums			Nonsyphilitic Serums		
Authors	Strains	Preparation	Number Tested	Per Cent Positive	Per Cent Positive, Wassermann	Number Tested	Per Cent Positive	Per Cent Positive, Wassermann
Noguchi[1a]	Noguchi	Saline	20	45	90	7	0	0
Craig and Nichols[1b]	Noguchi	Alcoholic	55	80	86	16	0	0
Kolmer, Williams and Laubaugh[1c]	Noguchi	Saline	81	44	99	79	0	0
Kolmer, Williams and Laubaugh[1c]	Noguchi	Alcoholic	56	21.2	....	79	0	0
Kolmer and Broadwell[1d]	Noguchi	Saline	35	31.4	88.6	7	0	0
Beck[5]	Reiter	Saline	542	89.3	64.2	496	1.6*	1.2*
Beck[5]	Kasan	Saline	542	96.3				
Beck[5]	Kroó	Saline	542	79.1				
Kolmer, Kast and Lynch[7a]	Nichols-Hough	Saline	139	72	81.3	114	22.9	0
Kolmer, Kast and Lynch[7a]	Noguchi	Saline	139	89.4	....	114	38.7	
Kolmer, Kast and Lynch[7a]	Kroó	Saline	139	92.1	....	114	61.4	
Kolmer, Kast and Lynch[7b]	Reiter	Saline	11	100.0	100	11	27.2	0

* Average with all three strains.

Undoubtedly antigens prepared of the Reiter and Kazan strains have proved most sensitive, with antigens of the Kroó and Noguchi strains ranking next in sensitivity. Under the circumstances if antigens of cultivated S. pallida ultimately find a place of practical value in the serologic diagnosis of syphilis, it would appear that they should be prepared of the Reiter or Kazan strains and preferably by a mixture of the two.

The method of preparation is also of importance. Evidently saline suspensions are more antigenic than alcoholic extracts, although Klop-

7. (*a*) Kolmer, J. A.; Kast, C. C., and Lynch, E. R.: Studies on the Role of Spirochaeta Pallida in the Wassermann Reaction: I. Complement Fixation in Syphilis, Leprosy, and Malaria with Spirochetal Antigens, Am. J. Syph., Gonor. & Ven. Dis. **25**:300, 1941; (*b*) II. The Relation of Spirochetal Antibodies to the Wassermann Reagin, ibid. **25**:412, 1941. (*c*) Beck.[5] Eagle and Hogan.[6]

stock,[8] as well as Höltzer and Popoff,[2e] have long maintained that the latter are satisfactory. Gaehtgens [4] stated that suspensions of the whole spirochetes in 0.3 per cent phenolized saline solution are superior to extracts of the organisms and that they keep well in the refrigerator up to six months, or at 37 C. for two months, although he emphasized the need for daily or frequent titration because of slow deterioration. Wadsworth, Van Amstel and Brigham,[9] however, have observed that antigenic substances are not readily extractable from S. pallida by ethyl alcohol, and under the conditions there appears to be a consensus that the antigens are best prepared of suspensions of whole organisms in phenolized saline solution.

As shown in table 2, a large number of reports [10] have been made on the results of complement fixation tests employing as antigen "palligen,"

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8. Klopstock, F.: Die Entstehung der syphilitischen Blutveränderung und ihr Nachweis mittels alkoholischen Spirochätenextrakts, Deutsche med. Wchnschr. **52**:226, 1926; **53**:1261, 1927.

9. Wadsworth, A. B.; Van Amstel, J. E., and Brigham, M. W.: The Preparation of Antigens from Cultures of Treponema Pallidum, J. Immunol. **19**: 289, 1930.

10. (*a*) Gaehtgens, W.: Weitere Erfahrungen über das wässerige karbolisierte Pallidaantigen für den serologischen Luesnachweis, Zentralbl. f. Bakt. (Abt. 1) **118**:26, 1930; (*b*) Weitere Untersuchungen über die Pallidareaktion insbesondere ihre Beziehungen zur W R, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**: 527, 1932. (*c*) Bender, E., and Bruns, H.: Der Wert der "Pallidareaktion" für den serologischen Luesnachweis, Klin. Wchnschr. **15**:640, 1936. (*d*) Döhnert, H. R.: Ueber die Stellung der Pallida-Reaktion nach Gaehtgens in der serologischen Diagnostik syphilitischer Erkrankungen, ibid. **15**:1406, 1936. (*e*) Frieboes, W., and Zündel, W.: Erfahrungen mit der Pallidareaktion, Arch. f. Dermat. u. Syph. **175**:255, 1937. (*f*) Fritzsche, G.: Untersuchungen mit dem Pallida-Antigen zur W R (Pallida-Reaktion nacht Gaehtgens) bei cerebral-luetischen Erkrankungen, Dermat. Wchnschr. **101**:1571, 1935. (*g*) Grüneberg, T.: Erhöhte Empfindlichkeit des W R bei Verwendung spezifischen Antigens (Pallida-Reaktion nach Gaehtgens), ibid. **99**:1330, 1934; (*h*) Der Wert der Pallidareaktion nach Gaehtgens für die Diagnose und prognostisch-therapeutische Beurteilung der Syphilis, Deutsche med. Wchnschr. **62**:465, 1936. (*i*) Heinemann, H.: Ueber die praktische Brauchbarkeit der Pallidareaktion im Arbeitskreis des Tropenarztes, Arch. f. Schiffs- u. Tropen-Hyg. **36**:9, 1932; (*j*) Untersuchungen mit der Pallidareaktion, Dermat. Wchnschr. **94**:680, 1932. (*k*) Marquardt, F.: Spirochätenextrakt als Antigen zur Wassermannschen Reaktion im Blut und Liquor, ibid. **91**: 1591, 1930. (*l*) Schlesmann, C.: Das Zentrifungierverfahren und die Schüttelmethode mittels Meinickes neueren Klärungsextrakten als Schnellreaktionen zum Luesnachweis an inaktiven Seren, Zentralbl. f. Bakt. (Abt. 1) **124**:384, 1932; (*m*) Der serologische Luesnachweis mit dem Kahnextrakt im Zentrifungierverfahren, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:467, 1934. (*n*) Vohwinkel, K. H.: Ueber die Pallida-Antigen-Reaktion, Med. Klin. **29**:428, 1933. (*o*) Erickson, P. T., and Eagle, H.: Spirochete Complement Fixation Reaction Compared with the Eagle and Wassermann Procedures, Ven. Dis. Inform. **21**:31, 1940. (*p*) Eagle and Hogan.[6]

which is commercially prepared of the Reiter strain under the supervision of Gaehtgens [11] in the Sächsischer Serumwerk at Dresden, Germany. Of the total of 13,636 tests with syphilitic serums summarized in this table, the incidence of positive reactions has varied from 44.5 to 100 per cent, with an incidence of positive Wassermann reactions varying from 30.4 to 100 per cent, although the sensitivity of the latter is difficult to express because of the variations in the technic employed by different investigators.

The high specificity of this antigen is also indicated by the fact that in tests employing the serums of 36,255 presumably nonsyphilitic

TABLE 2.—*Complement Fixation by "Palligen" (Reiter Strain) and Syphilitic and Nonsyphilitic Serums* *

Authors	Syphilitic Serums			Nonsyphilitic Serums		
	Number Tested	Per Cent Positive, Palligen	Per Cent Positive, Wassermann	Number Tested	Per Cent Positive, Palligen	Per Cent Positive, Wassermann
Gaehtgens and Otto[3a]	469	68.0	51.0	1,536	0.4	0.9
Gaehtgens [3b]	1,143	64.3	46.5	3,991	1.3	1.4
Gaehtgens [4]	1,831	65.0	45.0	6,662	1.7	1.3
Gaehtgens [10a]	1,108	67.4	53.0	5,583	1.8	0
Gaehtgens [10b]	1,185	66.0	50.0	2,796	0.85	0
Bender and Bruns [10c]	949	44.5	30.4	288	1.2	0
Döhnert [10d]	397	69.3	41.3	856	0	0
Frieboes and Zündel [10e]	729	62.8	54.2	2,009	1.84	0.25
Fritzsche [10f]	140	88.8	53.6	872	0.8	0.8
Grüneberg [10g]	823	85.4	77.0	981	1.4	0
Grüneberg [10h]	1,729	85.1	61.0	2,851	0	0
Heinemann [10i]	146	93.0	62.0	—	—	—
Heinemann [10j]	119	89.0	66.0	896	0	0
Marquardt [10k]	158	73.0	58.0	907	0.4	0
Schlesmann [10l]	614	66.2	53.7	436	2.9	2.7
Schlesmann [10m]	1,314	77.9	57.7	3,086	1.9	1.7
Vohwinkel [10n]	284	88.4	53.6	1,962	0	0
Erickson and Eagle [10o]	490	85.0	68.5	528	3.4	0
Eagle and Hogan [6]	8	100.0	100.0	15	0	0

* Slightly modified from table given by Gaehtgens.[11]

donors the incidence of falsely positive reactions varied from 0 to 3.4 per cent, with an incidence varying from 0 to 2.7 per cent in the case of the Wassermann reaction. This subject of specificity, however, will be discussed shortly in more detail.

Much less information is available on the incidence of positive reactions with spirochetal antigens in relation to the stages of the disease and its treatment (table 3), but Beck [5] stated the belief that tests with these antigens have proved superior to the Wassermann and flocculation tests in all stages, and especially in the late latent stage, as well as for treated patients. These aspects, however, require further investigation.

11. Gaehtgens, W.: Die bisherigen Erfahrung mit der Pallidareaktion zum serologischen Luesnachweis, Arch. f. Dermat. u. Syph. **176**:42, 1938.

B. *With Syphilitic Spinal Fluids.*—As shown in table 4, antigens of S. pallida and especially "palligen" have also proved highly sensitive in tests employing the cerebrospinal fluids of syphilitic donors, with an incidence of positive reactions varying from 66.6 to 100 per cent and an incidence of positive Wassermann reactions varying from 82 to 100

TABLE 3.—*Percentage of Positive Complement Fixation Reactions with Spirochetal Antigens in the Different Stages of Syphilis*

	Beck [5]			Kolmer, Kast and Lynch [7a]						
Stage of Syphilis	Number Tested	Combined Strains *	Wassermann	Number Tested	Nichols-Hough	Noguchi	Kroó	S. Macrodentium	S. Microdentium	Wassermann
Early untreated †	122	89.3	83.6	11	81.8	91	73.6	73.6	91	63.7
Early treated	104	52.8	28.8							
Latent untreated ‡	28	96.4	64.3	14	71.4	71.4	71.4	71.4	100	78.5
Latent treated	105	50.5	32.4							
Tertiary untreated	31	96.7	93.5	22	54.6	81.8	90.9	90.9	90.9	81.8
Tertiary treated	15	100	73.5	86	78	96.5	97.6	93	100	88.4
Neurosyphilis	13	100	100							
Congenital	5	60	100	6	66.6	99.9	99.9	66.6	99.6	66.6

* Combined results with Reiter, Kroó, Kazan II and Noguchi strains.
† Primary and secondary stages.
‡ Early and late latent stages of syphilis.

TABLE 4.—*Complement Fixation by Spirochetal Antigens and Syphilitic and Nonsyphilitic Spinal Fluids*

	Syphilitic Spinal Fluids				Nonsyphilitic Spinal Fluids		
Authors	Number Tested	Strains	Per Cent Positive	Per Cent Positive, Wassermann	Number Tested	Per Cent Positive	Per Cent Positive, Wassermann
Fritzsche [10f]	55	Palligen	100	84			
Sagher [12a]	198	Palligen	100	82	255	0	0
Marquardt [12b]	38	Palligen	84				
Marquardt [10k]	47	Palligen	100	..	25	0	
Erickson and Eagle [10o]	26	Palligen	100	100	60	0	0
Kolmer, Kast and Lynch [7a]	15	Nichols-Hough	73.3	100	15	0	0
Kolmer, Kast and Lynch [7a]	15	Noguchi	66.6	..	15	0	
Kolmer, Kast and Lynch [7a]	15	Kroó	66.6	..	15	6.6	
Kolmer, Kast and Lynch [7a]	15	Reiter	93.3	..	15	6.6	
Kolmer, Kast and Lynch [7a]	15	S. macrodentium	93.3	..	15	6.6	
Kolmer, Kast and Lynch [7a]	15	S. microdentium	73.3	..	15	6.6	

per cent.[12] It will be observed, however, that the incidence of falsely positive reactions with "palligen" antigen and nonsyphilitic spinal fluids

12. (*a*) Sagher, F.: Ueber klinische Verwertbarkeit des Palligens bei der Liquoruntersuchung, Arch. f. Dermat. u. Syph. **175**:443, 1937. (*b*) Marquardt, F.: Die Spezifität des Spirochätenextraktes in der serologischen Diagnostik syphilitischer Liquorveränderungen, München. med. Wchnschr. **81**:1229, 1934. (*c*) Fritzsche.[10f] Marquardt.[10k] Erickson and Eagle.[10o] Kolmer, Kast and Lynch.[7a]

was lower than with serums. Berings [13] reported that in 2,327 tests conducted with "palligen" as antigen there were no nonspecific reactions.

C. *With Syphilitic Rabbit Serum.*—Not without interest are the results reported on complement fixation tests with spirochetal antigens and the serums of syphilitic rabbits. As shown in table 5, the early investigations of Noguchi [1a] and of Craig and Nichols [1b] showed no positive reactions with the serums of rabbits yielding 40 to 100 per cent positive Wassermann reactions. Later investigations by Kolmer, Kast and Lynch [14] and by Eagle and Hogan [6] have shown, however, that positive reactions occur, especially with antigens prepared of the Reiter strain. It will be observed that positive reactions also occurred with the serums of normal rabbits, in spite of precautions in technic

TABLE 5.—*Complement Fixation by Antigens of Cultivated S. Pallida and Syphilitic and Nonsyphilitic Rabbit Serums*

	Spirochetal Antigens		Syphilitic Serums			Nonsyphilitic Serums		
Authors	Strains	Preparation	Number Tested	Per Cent Positive	Per Cent Positive, Wassermann	Number Tested	Per Cent Positive	Per Cent Positive, Wassermann
Noguchi [1a]	Noguchi	Saline	5	0	100	5	0	0
Craig and Nichols [1b]	Noguchi	Alcoholic	5	0	40	4	0	0
Kolmer, Kast and Lynch [14]	Nichols-Hough	Saline	6*	16.6	66.6	8*	11.2	0
Kolmer, Kast and Lynch [14]	Reiter	Saline	6*	100.0	....	..	100.0	
Eagle and Hogan [6]	Palligen	Saline	18	90	90	23	87	35

* Tests conducted by the modified Kolmer test for rabbit serums.

to avoid the nonspecific reactions, which I believe are due to the presence of a natural group spirochetal antibody in rabbit serums as likewise in normal human serums.

SPECIFICITY OF ANTIGENS OF CULTIVATED S. PALLIDA

A. *With Nonsyphilitic Human Serums and Spinal Fluids.*—As shown in table 1, Beck [5] has reported an incidence of 1.6 per cent falsely positive reactions with antigens of S. pallida and the serums of presumably nonsyphilitic donors, but the incidence observed by Kolmer, Kast and

13. Berings, F.: Einige Besonderheiten bei der Behandlung der Lues, Ztschr. f. ärztl. Fortbild. **33**:486, 1936.

14. Kolmer, J. A.; Kast, C. C., and Lynch, E. R.: Studies in the Role of Spirochaeta Pallida in the Wassermann Reaction: III. Complement-Fixation and Agglutination in Syphilis with Antigens of Tissue Spirochaeta Pallida, Am. J. Syph., Gonor. & Ven. Dis., to be published.

Lynch [15] has been as high as 22.9 to 61.4 per cent with antigens of the Nichols-Hough, Noguchi, Kroó and Reiter strains, which they have ascribed to the presence in human serums of a natural group spirochetal antibody capable of fixing complement with antigens prepared of alleged cultures of S. pallida.

Eagle and Hogan,[6] however, observed no nonspecific reactions with the serums of 15 nonsyphilitic persons when "palligen" was used as antigen, and, as shown in table 2, the incidence reported by other investigators with this antigen has varied from 0 to 3.4 per cent, with the majority reporting a low incidence. I am unable to give an explanation for this marked difference in results, especially since the antigens employed by Kast, Lynch and myself [15] were used in amounts comparable to the bacterial antigens in relation to their anticomplementary activity. At all events, it is apparent that the spirochetal antigens should be carefully titrated at frequent intervals with syphilitic serum and used in amounts as small as consistent with antigenic activity in order to avoid falsely positive or nonspecific reactions, which I believe may occur as a result of the presence in human serum of a natural spirochetal complement-fixing antibody.

Undoubtedly these nonspecific reactions are much less likely to occur in tests employing spinal fluids (table 4), which is not unexpected, since it is well known that normal spinal fluids are usually devoid of natural antibodies.

B. *With Nonsyphilitic Rabbit Serums.*—As is well proved, the serums of normal rabbits frequently yield falsely positive Wassermann reactions unless special precautions are taken in the way of heating them at 62 C. for thirty minutes instead of at 55 C. and using 4 units of complement instead of 2 (Kolmer). They also yield falsely positive flocculation reactions. But even under these technical conditions it is interesting to observe (table 5) that from 11.2 to 100 per cent have shown positive reactions with spirochetal antigens, while yielding negative Wassermann reactions. They likewise contain natural agglutinin for S. pallida, to which further reference will be made.

As shown by Beck,[5] the spirochetal antibody in human serums is more thermoresistant (63 C. for thirty minutes) than the reagin involved in the Wassermann and flocculation reactions; and since rabbit serums heated at 62 C. give negative Kolmer-Wassermann reactions but positive spirochetal complement fixation reactions, this observation has been confirmed in so far as normal rabbit serum is concerned.

It is apparent, therefore, that normal rabbit as well as normal human serums contain a natural spirochetal antibody responsible for complement fixation reactions with various spirochetal antigens; but even though in rabbit serums it resists heating at 62 C., this is not true of the

15. Kolmer, Kast and Lynch, footnote *7a* and *b*.

Wassermann reagin, which indicates that the spirochetal antibody and the Wassermann reagin may be separate substances. Furthermore, as will be shortly discussed, the absorption of rabbit serums with spirochetes removes the spirochetal antibody but not the reagin involved in the mechanism of the Wassermann and flocculation reactions. Under the circumstances it does not appear that this natural spirochetal antibody is responsible for the falsely positive Wassermann reactions when alcoholic extracts of heart or other mammalian tissue are employed as antigen.

C. *Natural Group Spirochetal Antibody.*—That human serums may contain a natural group spirochetal antibody is also shown by the results of complement fixation tests with antigens of various cultivated spirochetes other than S. pallida (table 6).

TABLE 6.—*Complement Fixation by Antigens of Cultivated Control Spirochetes and Syphilitic and Nonsyphilitic Human Serums*

Authors	Spirochetal Antigens	Syphilitic Serums		Nonsyphilitic Serums	
		Number Tested	Per Cent Positive	Number Tested	Per Cent Positive
Craig and Nichols [1b]	S. pertenuis	33	50	16	0
Craig and Nichols [1b]	S. microdentium	39	72	16	0
Beck [5]	Leptospira ictero-haemorrhagiae	102	1		
Beck [5]	S. dentium	407	50.2	366	4.4
Kolmer, Kast and Lynch [7a]	S. macrodentium	139	86.3	114	61.4
Kolmer, Kast and Lynch [7a]	S. microdentium	139	97.8	114	79.4
Kolmer, Kast and Lynch [7a]	Leptospira canicola	3	0	3	0
Kolmer, Kast and Lynch [7b]	S. microdentium	11	100	11	100

Beck [5] observed 4.4 per cent positive reactions with an antigen of an oral spirochete (Spirochaeta dentium) and Gaehtgens [3] also reported a low incidence of positive reactions with antigens of this organism. Kolmer, Kast and Lynch,[15] however, observed as high as 61.4 per cent positive reactions with an antigen of Spirochaeta macrodentium and 79.4 to 100 per cent with an antigen of Spirochaeta microdentium. As previously stated, they expressed the belief that this natural group antibody may be largely responsible for positive reactions obtained with syphilitic serums when antigens of cultivated S. pallida are employed; and, as will be shortly discussed, similar results have been observed in agglutination tests, which are of great interest, since it is practically proved that complement fixation and agglutination of bacteria are due to the same antibody.

COMPLEMENT FIXATION WITH SPIROCHETAL ANTIGENS IN MALARIA AND LEPROSY

Since it is well proved that positive Wassermann and flocculation reactions may occur in nonsyphilitic persons with malaria or leprosy,

the results of complement fixation tests with spirochetal antigens in these diseases are of great interest, as is the question of whether or not they possess sufficient specificity for permitting the identification of biologic false Wassermann and flocculation reactions of malarial or leprous patients in the absence of syphilis.

Nagell [16] has reported that the spirochetal complement fixation reaction was only rarely positive in malarial patients, including those yielding positive Wassermann and flocculation reactions, while Cappelli [17] reported that the serums of nonsyphilitic leprous patients regularly gave negative reactions with spirochetal antigens prepared of the Reiter strain

TABLE 7.—*Complement Fixation by Spirochetal Antigens in Serums of Persons with Malaria and with Leprosy*

	Malaria				Leprosy		
Authors	Number Tested	Strain	Per Cent Positive	Per Cent Positive, Wassermann	Number Tested	Per Cent Positive	Per Cent Positive, Wassermann
Gaehtgens [4]	21*	Palligen	9.5	81			
Heineman [10]	54	Palligen	16.6	....	3	66.6	—
Kolmer, Kast and Lynch [7a]	14†	Nichols-Hough	93	64.3	23	21.7	39.1
Kolmer, Kast and Lynch [7a]	8	Noguchi	87.5	....	23	21.7	
Kolmer, Kast and Lynch [7a]	14	Kroó	85.7	....	23	39.1	
Kolmer, Kast and Lynch [7a]	14	Microdentium	100	....	23	95.6	
Kolmer, Kast and Lynch [7a]	14	Macrodentium	71.4	....	23	17.4	
Eagle, Hogan, Mohr and Black [19]	..	.....	....	....	37‡	16.2	67.6
Eagle, Mays, Hogan and McBurney [18]	11	Reiter, Kazan	54.5	27.2			

* Induced malaria.
† Five cases of natural and 9 of induced malaria.
‡ Palligen employed as antigen. The spinal fluids of 10 patients gave negative Wassermann and spirochetal reactions.

of S. pallida. But, as shown in table 7, this has not been the experience of other investigators. Gaehtgens [4] observed 9.5 per cent, and Eagle, Mays, Hogan and McBurney [18] 54.5 per cent positive reactions in malaria with "palligen" antigen, while Kolmer, Kast and Lynch [7a] observed 85.7 to 93 per cent positive reactions with antigens prepared of three strains of cultivated S. pallida and 71.4 to 100 per cent positive

16. Nagell, H.: Ueber das Vorkommen unspezifischer Hemmungen bei der Wassermannschen Reaktion, Dermat. Wchnschr. **90**:795, 1930.

17. Cappelli, E.: La "pallidareazione" di Gaehtgens sul sieri lebbrosi; contributo allo studio dell' essenza della r. Wassermann, Gior. di batteriol. e immunol. **22**:245, 1939.

18. Eagle, H.; Mays, J. R. S.; Hogan, R. B., and McBurney, L. E.: The Reactivity of the Serum of Malarial Patients with Spirochetal Suspension, Am. J. Syph., Gonor. & Ven. Dis. **25**:406, 1941.

reactions with antigens of S. macrodentium and S. microdentium, respectively. They have attributed the positive spirochetal reactions partly to the presence of the natural group spirochetal antibody in human serums, but undoubtedly the reactions are increased by natural or induced malarial infection. At all events, it is obvious that the spirochetal complement fixation reaction does not permit the serologic differentiation of syphilis and malaria.

In leprosy Heinemann [10j] observed 66.6 per cent positive reactions with "palligen" as antigen, and Kolmer, Kast and Lynch [7a] observed from 21.7 to 39.1 per cent positive reactions with antigens of three strains of S. pallida in a group of 23 presumably nonsyphilitic lepers giving 39.1 per cent positive Kolmer-Wassermann reactions. With antigens of S. macrodentium and S. microdentium the incidence of positive reactions varied from 17.4 to 95.6 per cent, respectively; so these investigators attributed the positive reactions partly to the presence of natural group spirochetal antibody.

Eagle, Hogan, Mohr and Black,[19] however, observing but 16.2 per cent positive reactions with antigens of the Reiter and Kazan strains of S. pallida in a group of 37 lepers giving 67.6 per cent positive Wassermann reactions, stated the belief that the spirochetal complement fixation test permits the identification as biologic false reactions of most of the positive Wassermann and flocculation reactions observed in nonsyphilitic leprous patients. This, however, requires further investigation, but I personally doubt that it is possible. Incidentally, it may be mentioned that Heineman [10j] also observed 93.7 per cent positive reactions with "palligen" antigen in a group of 64 patients with frambesia tropica, which is to be expected in this disease due to Spirochaeta pertenuis and giving a high incidence of positive Wassermann and flocculation reactions.

AGGLUTINATION OF CULTIVATED SPIROCHETES BY SYPHILITIC AND NORMAL SERUMS

A. *By Syphilitic and Normal Human Serums.*—Since it is highly probable that complement fixation and agglutination of spirochetes are due to the same spirochetal antibody, the results of agglutination tests with normal and syphilitic human and rabbit serums are not without additional interest.

Kolmer [20] was first to study agglutination of cultivated S. pallida (Noguchi strain) in 1913 and observed negative reactions with the

19. Eagle, H.; Hogan, R. B.; Mohr, C. F., and Black, S. H.: On the Reactivity of the Serum and Spinal Fluid of Leprous Patients with Spirochetal Suspensions, Am. J. Syph., Gonor. & Ven. Dis. **25**:397, 1941.

20. Kolmer, J. A.: Concerning Agglutinins for Treponema Pallidum, J. Exper. Med. **18**:18, 1913.

serums of 19 syphilitic patients in final dilutions of 1:20 to 1:640, while the serums of 10 nonsyphilitic persons gave negative reactions in a dilution of 1:20. Since then agglutination tests have been conducted with the Noguchi and five additional strains of cultivated S. pallida,[21] as shown in table 8. It will be observed that the highest titers were observed with the Reiter strain, which also gave the highest incidence of positive complement fixation reactions. But Kolmer, Kast and Lynch [7b] also observed decided agglutination of S. macrodentium (1:200 to 1:1,000)

TABLE 8.—*Agglutination of Cultivated S. Pallida by Syphilitic and Nonsyphilitic Human Serums*

		Syphilitic Serums			Nonsyphilitic Serums		
		Number	Results		Number	Results	
Authors	Strains	Tested	Reaction	Dilution	Tested	Reaction	Dilution
Kolmer [20].....	Noguchi	19	Neg.	1:20 to 1:640	10	Neg.	1:20
Kissmeyer [21a]....	Noguchi	50	Pos.	1:100	?	Pos.	1:50
Kolmer, Broadwell and Matsunami [21b]	Zinsser (A)	54	50 Pos.	1:2 to 1:80	20	10 Pos.	1:2
Kolmer and Broadwell [1d]	Zinsser (A)	45	34 Pos.	1:2 to 1:80	7	3 Pos.	1:2
Zinsser, Hopkins and McBurney [21c]	Zinsser (A)	127	50 Pos.	1:2 to 1:100	40	5 Pos.	1:2 to 1:10
Caldwell [21d].....	Noguchi, Zinsser (A)	160	112 Pos.	1:20 to 1:120			
Beck [5].....	Reiter, Kroó, Kazan II, Noguchi	25	25 Pos.	1:40 to 1:600	25	?	0 to 1:160
Eagle and Hogan [6]	Reiter (Palligen)	8	8 Pos.	1:8 to 1:64	15	15 Pos.	1:3 to 1:16
Kolmer, Kast and Lynch [7b]	Nichols-Hough	9	9 Pos.	1:10 to 1:20	10	10 Pos.	1:10 to 1:50
Kolmer, Kast and Lynch [7b]	Noguchi	10	10 Pos.	1:10 to 1:50	11	11 Pos.	1:10 to 1:20
Kolmer, Kast and Lynch [7b]	Kroó	11	11 Pos.	1:20 to 1:100	10	10 Pos.	1:10 to 1:50
Kolmer, Kast and Lynch [7b]	Reiter	11	11 Pos.	1:500 to 1:1,000	11	11 Pos.	1:500 to 1:1,000

and especially of S. microdentium (1:200 to 1:10,000) by syphilitic and nonsyphilitic human serums. In fact, the average agglutination

21. (*a*) Kissmeyer, A.: Agglutination der Spirochaeta Pallida, Deutsche med. Wchnschr. **41**:306, 1915 (*b*) Kolmer, J. A.; Broadwell, S., and Matsunami, T.: Agglutination of Treponema Pallidum in Human Syphilis, J. Exper. Med. **24**: 333, 1916. (*c*) Zinsser, H.; Hopkins, J. G., and McBurney, M.: Studies in Treponema Pallidum and Syphilis: V. Further Studies on the Relation of Culture Pallida to Virulent Pallida and on Reinfection Phenomena, ibid. **24**:561, 1916. (*d*) Caldwell, W. A.: The Immunity Reactions Against Cultivated Spironema Pallidum of General Paralytics Treated by Induced Malaria, Brit. J. Exper. Path. **11**:1, 1930. (*e*) Kolmer.[20] Kolmer and Broadwell.[1d] Beck.[5] Eagle and Hogan.[6] Kolmer, Kast and Lynch.[7b]

titers for the various strains were so similar that the agglutination test with cultivated spirochetes is without diagnostic value, as shown in table 9. In other words, the results of agglutination tests have confirmed those of complement fixation tests in showing the presence of a natural spirochetal antibody in normal human serums; and, as stated by Beck,[5] since the titers with some syphilitic serums are not higher than the highest titers found with normal serums, it is evident that the agglutina-

TABLE 9.—*Average Agglutination Titers*

Strains	Syphilitic Serums	Nonsyphilitic Serums
Nichols-Hough	1:22	1:22
Noguchi	1:21	1:18
Kroó	1:46	1:29
Reiter	1:773	1:700
S. macrodentium	1:610	1:360
S. microdentium	1:8,000	1:6,270

TABLE 10.—*Agglutination of Cultivated S. Pallida by Syphilitic and Nonsyphilitic Rabbit Serums*

		Syphilitic Serums			Nonsyphilitic Serums		
		Number	Results		Number	Results	
Authors	Strains	Tested	Reaction	Dilution	Tested	Reaction	Dilution
Kolmer [20]	Noguchi	..	.....	.....	4	4 Neg.	1:20
Zinsser and Hopkins [22a]	Zinsser (A)	..	.....	.....	9	9 Pos.	1:10
Blum [22b]	?	17	17 Pos.	1:10 to 1:100	25	25 Pos.	1:2 to 1:100
Eagle and Hogan [6]	Reiter (Palligen)	18	18 Pos.	1:4 to 1:128	23	23 Pos.	1:4 to 1:32
Kolmer, Kast and Lynch [22c]	Reiter	..	.....	.....	7	7 Pos.	1:100 to 1:500
Kolmer, Kast and Lynch [22c]	Kroó	..	.....	.....	4	4 Pos.	1:10 to 1:200
Kolmer, Kast and Lynch [22c]	Noguchi	..	.....	.....	4	4 Pos.	1:50 to 1:100
Kolmer, Kast and Lynch [22c]	Nichols-Hough	..	.....	.....	4	4 Pos.	1:50 to 1:200

tion test with cultivated spirochetes does not give the clearcut differentiation between normal and syphilitic serums which is required for diagnostic purposes. Whether or not an increase of spirochetal agglutinin occurs in malaria and leprosy cannot be stated, although Caldwell [21d] reported that in patients with dementia paralytica under treatment with induced malaria the titers were higher than in untreated patients.

B. *By Syphilitic and Normal Rabbit Serums.*—Relatively few studies of agglutination of cultivated S. pallida have been made with rabbit serums, but, as shown in table 10, a natural agglutinin undoubtedly exists in the serums of normal animals (1:2 to 1:500) and especially

for the Reiter strain.[22] Kolmer, Kast and Lynch [7b] also found normal rabbit serums to contain agglutinin for S. macrodentium (1:20 to 1:50) and for S. microdentium (1:10 to 1:200). Apparently, however, the agglutinin undergoes but a slight or doubtful increase in syphilitic orchitis of rabbits, being similar in this respect to the doubtful or slight increase which may occur in human syphilis.

AGGLUTINATION AND COMPLEMENT FIXATION BY VIRULENT TISSUE S. PALLIDA

All of the investigations so far considered have dealt with cultivated spirochetes. In so far as S. pallida is concerned it cannot be accepted with certainty that the cultures employed are the true organism of syphilis, although it is stated that the Kroó strain has proved virulent in its eightieth passage fifteen months after isolation.[5] Certainly the true nature of the cultures employed remains at present uncertain, but if the organisms are S. pallida there is also the possibility of dissociation in cultures with only nonvirulent variants surviving and proliferating along with a possible change in antigenic structure, similar to the S → R dissociation of many of the bacteria.

Agglutination of Virulent Tissue S. Pallida.—At least this possibility is suggested by the difference in agglutination of cultivated nonvirulent and virulent S. pallida obtained from syphilitic lesions. But it is hardly worth while to review the results of early investigations conducted with human syphilitic serums and spirochetes obtained from chancres or mucous patches except to state that while Hoffmann and von Prowazek [23] reported in 1906 that the serum of patients in the later stages of syphilis produced a diminution of motility of S. pallida, which was confirmed by Zabolotny and Maslakowetz [24] and by Scharnke and Ruete; [25] but contradictory results were observed by Landsteiner and Mucha,[26] who were unable to observe either immobilization or agglutination of tissue spirochetes by syphilitic serum.

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22. (*a*) Zinsser, H., and Hopkins, J. G.: Antibody Formation Against Treponema Pallidum-Agglutination, J. Exper. Med. **21**:576, 1915. (*b*) Blum, K.: Versuche über die Agglutination der Spirochaeta pallida, Ztschr. f. Immunitätsforsch. u. exper. Therap. **40**:491, 1924. (*c*) Kolmer, Kast and Lynch (footnote 7 *b* and 14). (*d*) Kolmer.[20] Eagle and Hogan.[6]

23. Hoffmann, E., and von Prowazek, S., cited by Neisser and Bruck: Immunisierungs-versuche (bei der Syphilis), Arb. a. d. k. Gsndhtsamte **37**:203, 1911.

24. Zabolotny, D., and Maslakowetz, A.: Beobachtungen über Beweglichkeit und Agglutination der Spirochaeta pallida, Centralbl. f. Bakt. (Abt. 1) **44**:532, 1907.

25. Scharnke and Ruete: Spirochäten, Serum und Liquor. Studien zur Pathogenese der Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:343, 1921.

26. Landsteiner, K., and Mucha, V.: Zur Technik der Spirochaetenuntersuchung, Wien. klin. Wchnschr. **19**:1349, 1906; abstracted, Centralbl. f. Bakt. (Abt. 2) **39**:540, 1907.

Kolmer, Kast and Lynch,[14] however, have recently reported that normal human serums agglutinated the virulent Nichols-Hough strain obtained from acute testicular syphilomas of rabbits in final dilutions of 1:50 to 1:100, while agglutination of the same strain after cultivation occurred in dilutions of 1:10 to 1:50 (table 8). Syphilitic human serums agglutinated the virulent tissue spirochetes of this strain in final dilutions as high as 1:500 to 1:1,000 but the cultivated organisms only at 1:10 to 1:20 (table 8). Under the conditions it appears, therefore, that the cultivated organisms have undergone a change in antigenic structure reducing their susceptibility to agglutination.

Similar results were observed with rabbits. The serums of normal animals agglutinated the virulent tissue spirochetes in final dilutions of 1:500, while the serums of syphilitic rabbits agglutinated them at 1:1,000. Since normal rabbit serums agglutinated the cultivated organisms in dilutions of 1:50 to 1:200 (table 10), it is apparent that these cultivated organisms probably represent a "rough" variant with reduced susceptibility to agglutination and complete loss of virulence.

Under the circumstances it appears that there is a more definite agglutination of virulent tissue S. pallida by the serums of both syphilitic human beings and syphilitic rabbits than of cultivated nonvirulent organisms. Furthermore Zinsser, Hopkins and McBurney[27] observed that the serums of rabbits and sheep treated with cultures of S. pallida agglutinated the cultivated spirochetes in high dilutions but failed to agglutinate virulent spirochetes from human lesions, which likewise indicated that cultivated spirochetes undergo a change in antigenic structure sufficient for rendering their antiserums more active against them than against virulent tissue spirochetes. At least the evidence indicating an increase of agglutinin for S. pallida in both human and rabbit syphilis is far more definite in tests employing virulent tissue S. pallida than in those employing cultures of the nonvirulent organisms, which was first definitely shown by Kolmer, Kast and Lynch.[14]

Complement Fixation with Antigens of Virulent Tissue S. Pallida.—The same has been found true in complement fixation tests. Noguchi[1a] tested the serums of 5 rabbits with syphilitic orchitis employing as antigen a saline extract of testicular syphilomas and observed 1 positive reaction, but since a control extract also elicited a positive reaction the results are without significance. Noguchi also tested 20 syphilitic human serums and observed positive reactions in 12, but 10 of these serums also gave positive reactions with the control extract of normal testicular tissue.

27. Zinsser, H.; Hopkins, J. G., and McBurney, M.: Studies on Treponema Pallidum and Syphilis: IV. The Difference in Behavior in Immune Serum Between Cultivated Non-Virulent Treponema Pallidum and Virulent Treponemata from Lesions, J. Exper. Med. **23**:341, 1916.

Kolmer, Kast and Lynch,[14] however, secured the spirochetes of the Nichols-Hough strain from testicular syphilomas in rabbits in practically pure suspensions in saline solution by a painstaking technic, and this antigen gave positive complement fixation reactions with 88 per cent of the serums of 25 syphilitic patients, while 72 per cent of the serums of 139 syphilitic serums gave positive reactions with an antigen of the cultivated spirochetes of the same strain (table 1). In tests employing 22 nonsyphilitic human serums the incidence of positive reactions with the antigen of tissue spirochetes was 22.5 per cent, while 22.9 per cent of 114 serums gave positive reactions with an antigen of the cultivated spirochetes of the same strain (table 1). A control extract of normal testicular tissue of rabbits prepared as nearly as possible in the same manner and used in the same dose gave completely negative reactions with both syphilitic and nonsyphilitic human serums; so the positive reactions observed with the tissue spirochetes can be reasonably ascribed to the organisms.

Under the circumstances it appears practically certain that in both human and rabbit syphilis there are produced antibodies for virulent tissue S. pallida (agglutinating and complement fixing), in confirmation of the observations of Turner,[28] who found that in syphilis of rabbits there develop specific humoral antibodies (which in his experiments were demonstrated by a "protection test") associated with a high degree of acquired immunity to the disease.

COMPARISON OF DIFFERENT STRAINS OF CULTIVATED S. PALLIDA

As previously stated, of the six strains of alleged cultivated S. pallida employed by various investigators in complement fixation and agglutination tests, that of Reiter appears to be most susceptible to antibody action. Immune spirochetal antibodies are readily prepared by the treatment of rabbits with living or killed cultures,[29] and these immune serums have been employed by several investigators in agglutination and complement fixation tests for studying the relations of the cultivated strains of S. pallida to each other and to other spirochetes. Thus Zinsser, Hopkins and McBurney[21c] observed that the serums of immunized rabbits treated with Zinsser's strain A agglutinated the homologous strain at 1:2,000 but two of the Noguchi strains at 1:400 and 1:1,000 respectively, Spirochaeta calligyrum at 1:4,000, Spirochaeta

28. Turner, T. B.: Protective Antibodies in the Serum of Syphilitic Rabbits, J. Exper. Med. **69**:867, 1939.

29. (*a*) Cohn, A.: Ueber Schutzstoffe bei der experimentellen Syphilis, Klin. Wchnschr. **8**:886, 1929. (*b*) Plaut, F., and Kassowitz, H.: Zur Frage der immunologischen Abgrenzung von Pallidastämmen, ibid. **9**:1396, 1930. (c) Kolmer, Williams and Laubaugh.[1c] Klopstock.[2d] Beck.[5] Zinsser, Hopkins and McBurney.[21c]

refringens at 1:200 and S. microdentium at 1:1,000. By complement fixation, agglutination and absorption tests Beck [5] observed the complete serologic identity of the Kazan and Reiter strains in confirmation of the observations of Höltzer and Ssuschkowa,[30] while the Noguchi and Kroó strains of S. pallida and an oral spirochete differed in some degree from these two strains and from each other. Kolmer, Kast and Lynch [7b] immunized rabbits with killed cultures of the Nichols-Hough, Noguchi and Kroó strains of S. pallida as well as with S. macrodentium and S. microdentium, and in cross agglutination and complement fixation tests they observed that all were serologically related. The Nichols-Hough and Noguchi strains were found to be closely related, and the serum of a rabbit immunized against the Nichols-Hough strain gave almost as strongly positive complement fixation reactions with the Reiter strain as with the homologous strain.

Tables 1 and 8 also show a biologic relation not only among different strains of cultivated S. pallida in complement fixation and agglutination tests but likewise a relation to the oral spirochetes (S. macrodentium and S. microdentium) in both syphilitic and normal human serums. Under the circumstances it may be that the natural spirochetal antibody found in normal human serums is largely derived from antigenic stimulation by the oral spirochetes and even by S. refringens.[21c]

RELATION OF THE SPIROCHETAL ANTIBODY TO THE WASSERMANN REAGIN

This brings me to a discussion of the important and interesting subject of the relation of the spirochetal antibody to the so-called Wassermann reagin, which reacts with mammalian tissue lipids to give positive Wassermann and flocculation reactions in syphilis, malaria and leprosy. This necessarily also includes a discussion of the chemistry of spirochetal antigens.

I may state at the outset that Gaehtgens,[31] as well as Kroó, Schultze and Zander [32] and Kolmer, Kast and Lynch,[7b] on the basis of absorption tests of syphilitic serums with tissue lipids for the removal of the Wassermann reagin and with spirochetes for the removal of the spirochetal antibodies, came to the conclusion that the two are entirely separate and have nothing in common. Apparently Beck [5] reached the same

30. Höltzer, R. R., and Ssuschkowa, E. G.: Zur Frage über das Wesen der Wassermann-Reaktion, Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:81, 1930.

31. Gaehtgens, W.: Ueber die antigene Wirkung von Pallidasuspionen in carbolisierter Kochsalzlösung, Med. Klin. **25**:390, 1929.

32. Kroó, H.; Schultze, F. O., and Zander, I.: Untersuchungen über die Immunitätsvorgänze bei Syphilis: II. Die syphilitische Blutveränderung, Klin. Wchnschr. **8**:783, 1929.

conclusion, while Eagle and Hogan [6] have stated the belief that the substances are identical, or, in other words, that positive Wassermann and flocculation reactions as well as positive spirochetal complement fixation reactions are due to spirochetal antibodies.

Thus, Beck [5] observed that the absorption of syphilitic serum with Wassermann antigen removed the reagin but not the complement-fixing antibody or agglutinin for the Reiter strain of S. pallida. On the other hand, absorption with the spirochetes removed all of the spirochetal antibodies but only slightly reduced the reagin. Furthermore, absorption with an alcoholic extract of the Reiter strain of spirochetes removed the reagin but not the spirochetal antibodies, which showed thereby a relation between the lipids of the spirochetes and the lipids of the Wassermann antigen (alcoholic extract of heart).

Exactly similar results have been observed by Kolmer, Kast and Lynch.[7b] Absorption of human syphilitic serum with Kahn antigen removed the reagin concerned in the Wassermann and flocculation reactions in confirmation of the results which I observed thirteen years ago [33] but did not remove the spirochetal antibodies (complement-fixing antibody and agglutinin). Absorption with the Reiter strain of cultivated S. pallida, on the other hand, removed the spirochetal antibodies but not the reagin. Furthermore, absorption of normal rabbit serum with the Reiter spirochetes removed the spirochetal antibodies but not the reagin giving positive Wassermann and flocculation reactions.

Eagle and Hogan,[6] however, have reported that absorption of human syphilitic serum with beef heart lipids removed all of the reagin but not the spirochetal antibodies. This is in agreement with the observations of Beck and myself. But they reported that absorption with the Reiter strain of spirochetes ("palligen") removed not only the spirochetal antibodies but the reagin as well, which was not the experience of Beck and myself. On the basis of their results Eagle and Hogan concluded that spirochetes contain a ubiquitous lipid also present in alcoholic extracts of beef heart and that the Wassermann, flocculation and spirochetal complement fixation reactions are due to spirochetal antibodies.

With this point of view I cannot agree. Furthermore, the immunization of rabbits with living and heat-killed strains of S. pallida (Nichols-Hough, Noguchi and Kroó) as well as with S. macrodentium and S. microdentium produced large amounts of spirochetal antibodies but not the reagin or "lipid antibody." [7b] Apparently the latter is produced only during syphilitic infection in so far as spirochetes are concerned.

Whether or not rabbits given injections of tissue lipids produce the reagin and spirochetal antibodies is undecided. Thirteen years ago I

33. Kolmer, J. A.: Serum Diagnosis by Complement Fixation, Philadelphia, Lea & Febiger, 1928, p. 57.

observed that rabbits given intravenous injections of alcoholic extracts of congenital syphilitic liver, of beef heart and of acetone-insoluble lipids of beef heart sometimes produced very small amounts of complement-fixing antibody specific for the tissue (human or beef) from which the extracts were prepared.[34] But since all of the extracts contained traces of protein, I concluded that the complement-fixing antibody produced was antiprotein since it is well established that protein-free lipids are not antigenic. Sachs, Klopstock and Weil,[35] however, have reported that tissue lipids treated with syphilitic serum, followed by removal of the excess of serum by washing the flocculi, produced the reagin when injected into rabbits. Eagle and Hogan [6] confirmed this observation and likewise observed that the lipids produced spirochetal antibodies as well, which doubtless influenced them greatly in arriving at the conclusion that Wassermann and flocculation reactions as well as spirochetal complement fixation are due to spirochetal antibodies.

As previously stated, Beck [5] has claimed that when human syphilitic serum is heated at 63 C. for thirty minutes the spirochetal antibody resists destruction, whereas the Wassermann reagin is destroyed. Eagle and Hogan,[6] however, have found no difference in thermoresistance. Kolmer, Rule and Trist [36] reported that heating human serum at 62 C. for thirty minutes results in a decided loss of Wassermann reagin, and I have found the same to be true in the case of the spirochetal antibody, although the destructive effects are not as great.

With normal rabbit serum, however, the differences in thermoresistance of the substance yielding positive Wassermann reactions and natural spirochetal antibody have been striking, as previously discussed. Thus, the former is destroyed at 62 C. while the latter is resistant. However, the substance sometimes occurring in normal rabbit serum yielding positive Wassermann and flocculation reactions may not be identical with the reagin occurring in human syphilitic serum.

At all events, it appears that this matter of the thermoresistance of reagin and of spirochetal antibody requires further investigation, as does the question of their being separate or identical substances, but I believe that at present the preponderance of evidence is in favor of regarding the reagin as entirely separate and distinct from the spirochetal complement-fixing and agglutinating antibody.

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34. Kolmer,[33] p. 68.

35. Sachs, H.; Klopstock, A., and Weil, A. J.: Die Entstehung der syphilitischen Blutveränderung, Deutsche med. Wchnschr. **51**:589, 1925.

36. Kolmer, J. A.; Rule, A. M., and Trist, M. E.: Studies in the Standardization of the Wassermann Reaction: XIII. The Influence of Heating Serum upon Complement Fixation in Syphilis, Am. J. Syph. **4**:641, 1920.

CHEMISTRY OF SPIROCHETAL ANTIGENS

Undoubtedly, however, complement fixation by syphilitic serum and spirochetal antigens is partly due to a fixation of complement by the Wassermann reagin and the lipids of spirochetes. Williams, Laubaugh and I expressed this opinion on the basis of experiments about twenty-eight years ago,[1c] and since then it has been confirmed by Beck and other investigators.

But it does not appear reasonable to assume that spirochetes contain enough lipids to account alone for the fixation of complement by Wassermann reagin and spirochetal antigens, although this is to be admitted as a possibility in view of the fact that extremely small amounts of the actively antigenic substances in alcoholic extracts of beef heart suffice for yielding positive Wassermann reactions.[37] Furthermore, there can be no doubt that alcoholic extracts of cultivated S. pallida are capable of complement fixation with the Wassermann reagin in syphilitic human serum, but whether or not the fixing principle in the extracts is solely spirochetal lipid has not been determined.

Beck [5] has digested the Reiter strain of cultivated S. pallida with trypsin and found the digest highly antigenic in complement fixation tests with rabbit antispirochetal serum and with syphilitic human serum; on this basis he assumed that spirochetes contain a specific antigen which is not protein in nature. But a precipitate which he called F68, obtained by adding alcohol to the trypsin digest, gave positive complement fixation reactions with antispirochetal serum but not with human syphilitic serum, for which he had no explanation. Kolmer, Kast and Lynch [14] have confirmed Beck's observations with trypsin digests of the Reiter strain as well as with the Nichols-Hough strain. But while Beck observed that an alcoholic precipitate of the trypsin digest of the Reiter strain (F68) reacted negatively with human syphilitic serum, we found that while one of our F68 fractions of this strain also failed to fix complement with human serum, other F68 fractions of the strain did so as well as F68 fractions of the Nichols-Hough strain. The one F68 fraction failing to cause fixation of complement was prepared by washing the spirochetes with acetone, as employed by Beck, instead of by extracting in a Soxhlet apparatus in the making of the tryptic digest from which it was prepared, but whether or not this technical difference along with the fact that the F68 fraction was protected from light accounts for the results I am unable to state. At all events, according to Beck, the trypsin digests of spirochetes carry the complete antigen, while the F68 fractions do not; but according to our results both the

37. Brown, H., and Kolmer, J. A.: Studies on the Chemical Constitution of the Antigenic Substance in Alcoholic Tissue Extracts Concerned in the Serum Diagnosis of Syphilis, J. Biol. Chem. **137**:525, 1941.

trypsin digests and the F68 fractions were completely antigenic, although the former were observed to be more antigenic than the latter. Under the conditions it seems to me that both fractions probably contain sufficient lipids to react with the Wassermann reagin, while both may also contain some other antigenic principle, presumably nonprotein in nature (Beck), with which spirochetal antibody reacts.

PRACTICAL VALUE OF SPIROCHETAL ANTIGENS IN THE SEROLOGIC DIAGNOSIS OF SYPHILIS

In conclusion, I prefer to state that the practical value of spirochetal antigens in the serologic diagnosis of syphilis has not yet been determined. However, one cannot fail to be favorably impressed by the results summarized in table 2 obtained with antigen of the Reiter strain, commercially known as "palligen." But the results have been largely expressed and evaluated by comparison with the results of Wassermann and various flocculation tests, and much depends on the technic of these tests. If it is ultimately shown that tests with spirochetal antigens are not superior to the Wassermann and flocculation tests when the latter are properly conducted by methods possessing the maximum of sensitivity consistent with specificity, it is not likely that they will find a place in the practical serologic diagnosis of syphilis. In the final analysis they must be evaluated not so much in relation to the Wassermann and flocculation tests as to the clinical status of the donors and to the various stages of syphilis with and without treatment. But they are certainly worthy of further study, and it is my hope to include a spirochetal antigen prepared of the whole spirochetes of the Reiter strain in 0.3 per cent phenolized saline solution in the next United States Serologic Survey, since the syphilitic and nonsyphilitic donors are selected and classified with such care and skill as to render the comparative results of great value.[38]

At all events, I believe that the dose of spirochetal antigen employed must be determined very carefully and at frequent intervals, by titration not only for anticomplementary activity but also for fixability with syphilitic serum, with the hope that the fixing dose will be four or

38. With the permission of the committee on the evaluation of serodiagnostic tests for syphilis of the United States Public Health Service, I included an antigen of the Reiter strain of alleged S. pallida in the serologic survey conducted in Washington, D. C., in October 1941. The results will be included in the report of the committee, but it may be stated that this antigen gave 70.6 per cent positive reactions with the serums of syphilitic donors and 6.3 per cent falsely positive reactions with the serums of nonsyphilitic donors. With the spinal fluids of syphilitic donors 83.1 per cent positive reactions were observed, and with the spinal fluids of nonsyphilitic donors no nonspecific reactions were observed.

more times less than the anticomplementary unit, in order to avoid as far as possible falsely positive reactions due to natural spirochetal antibody.

Apparently suspensions of virulent S. pallida prepared from acute testicular syphilomas of rabbits are to be preferred to suspensions of cultivated strains; owing to technical difficulties, however, and to the small yield when the antigens are prepared with the minimum of tissue debris, it is not likely that they will prove of practical application in the serologic diagnosis of syphilis.

SUMMARY AND CONCLUSIONS

Complement fixation tests conducted with antigens of cultivated S. pallida, especially of the Reiter and Kazan strains, compare favorably in sensitivity with the Wassermann and flocculation tests in the serologic diagnosis of syphilis of human beings and rabbits, but their practical value in the diagnosis of the disease in its different stages and in relation to treatment has not been sufficiently defined.

Spirochetal complement fixation tests in syphilis of human beings and rabbits are not as specific as the Wassermann and flocculation tests, largely because of the presence in normal serum of natural spirochetal antibody.

This natural antibody as well as that produced in syphilis is of a group character reacting not only with cultivated S. pallida but with S. macrodentium, S. microdentium and other spirochetes.

Spirochetal complement-fixing antibody is increased in malaria and in leprosy, with a high incidence of positive complement fixation reactions in both diseases, especially in the former. Under the conditions it is improbable that the spirochetal complement fixation test will identify as biologic false reactions the positive Wassermann and flocculation reactions observed in nonsyphilitic persons with leprosy and malaria.

Normal human and rabbit serums also contain a natural group agglutinin for cultivated S. pallida and other spirochetes. The agglutinin undergoes some increase in syphilis but not sufficient for rendering the spirochetal agglutination test with cultivated spirochetes of diagnostic value in syphilis.

The results of agglutination and complement fixation tests with suspensions of virulent S. pallida obtained from acute testicular syphilomas of rabbits have indicated more definitely the production of these antibodies in syphilis of human beings and rabbits than tests employing suspensions of the cultivated spirochetes, which suggests that the latter have undergone dissociation into variants with a change in antigenic structure associated with a loss of virulence.

Complement fixation and agglutination tests with cultivated spirochetes have indicated the possible existence of serologic strains of S. pallida and also their biologic relation to S. macrodentium, S. microdentium and S. refringens.

Largely on the basis of absorption of syphilitic human serum with tissue lipids and suspensions of cultivated S. pallida, the preponderance of evidence is in favor of regarding the Wassermann reagin and spirochetal antibody as separate entities which may coexist in serum.

Undoubtedly the lipids of S. pallida are important in complement fixation by the Wassermann reagin. Whether spirochetal antibody reacts with them is unknown, but it has been suggested that it fixes complement with some other constituent of spirochetes, of a nonprotein nature.

The practical value of antigens of cultivated S. pallida in the serologic diagnosis of syphilis and in relation to the treatment of the disease cannot be stated at present, but they are worthy of further study. If such strains are employed, antigens of whole spirochetes in phenolized saline solution appear to be advisable. The Reiter or Kazan strains are preferred, and a mixture of the two may be advisable. The amount employed should be the minimum giving positive reactions with human syphilitic serum, in order to avoid falsely positive reactions with natural spirochetal antibody as much as possible. Suspensions of virulent tissue spirochetes are preferred, but owing to technical difficulties in their preparation they probably cannot be employed.

A NEW BISMUTH COMPOUND IDENTICAL IN CHEMICAL ORIGIN WITH SOBISMINOL MASS

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The successful oral use of sobisminol mass (N. N. R.) in antisyphilitic treatment has stimulated the development of closely related bismuth complexes as possible substitutes. Such complexes might shed light on the relation between the chemical nature and the gastrointestinal absorption and actions of bismuth. This report presents results of a study on the gastrointestinal absorption and toxicity of a new bismuth compound prepared from the same ingredients which enter into the composition of sobisminol mass [1] and sobisminol solution (N. N. R.). Both sobisminol mass and sobisminol solution are absorbed from the alimentary canal, and, as far as known, both contain the same active bismuth complex chemically.

The new compound was prepared by Dr. William T. Miller during his tenure of a Lilly fellowship in the Stanford University department of chemistry. Dr. Miller's original objective was to determine the chemical nature of sobisminol mass, but he could not isolate any pure products from the reaction between sodium bismuthate and triisopropanolamine in propylene glycol, the ingredients of sobisminol mass.[2] Therefore, he carried out the reaction between the sodium bismuthate and triisopropanolamine in xylene instead of in propylene glycol and obtained a definite chemical compound, which he has named sodium bismuthyl triisopropanolamine. The same compound was produced when bismuth hydroxide was used instead of the bismuthate. The compound prepared with the hydroxide was used in our experiments.

Miller's product is a white crystalline hydrate, soluble in water and propylene glycol, and contains 41.8 per cent bismuth, which is about

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1. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sodium Bismuthate Soluble, Am. J. Syph., Gonor. & Ven. Dis. **21**:1, 1937.

2. Miller, W. T.: Some Complex Sodium Bismuth Salts of Triethanolamine and Triisopropanolamine, J. Am. Chem. Soc. **62**:2707, 1940.

twice that contained in sobisminol mass. The compound gives a clear aqueous solution, but high dilution with water and boiling causes some turbidity. Boiling with an equal part of horse serum does not result in immediate precipitation, but the mixture gels on standing. Solutions of 3 and 10 per cent strengths are colorless when freshly prepared but on standing in stoppered containers exposed to daylight become yellowish brown in about thirty days and gradually form precipitates. This color is different from that of sobisminol solution in corresponding strengths. Sobisminol solution is a deep reddish brown, does not precipitate on standing, is stable when exposed to daylight and prevents heat coagulation of serum and other proteins. In other words, the solution of Miller's compound is less stable than sobisminol solution, even after the addition of an excess of triisopropanolamine or propylene glycol, or both. According to these properties in vitro, gastrointestinal absorption of Miller's product might be questionable. The answer was obtained by simple crucial tests in animals for direct absorption and toxicity of bismuth.

INTESTINAL ABSORPTION

Intestinal absorption was tested by introducing solutions of bismuth directly into ligated loops, 10 cm. in length, of the small intestines of laparotomized cats previously anesthetized with soluble pentobarbital U. S. P. (30 mg. per kilogram). Evidence of absorption was a positive reaction to a test for bismuth in urine collected directly from cannulated ureters. The short clinical method developed in this department was used in testing for bismuth.[3] Miller's product was used in 3 per cent and 10 per cent solutions, the total quantities of bismuth introduced being 60 and 100 mg., respectively. Sobisminol solution was used as control, the total quantity of bismuth being 60 mg., injected into an adjoining loop after the test with Miller's product had been completed.

Briefly, the results were as follows: With Miller's product no positive reactions were obtained for bismuth in the urines of 8 cats during test periods of four and five hours. On the other hand, with sobisminol solution positive reactions for bismuth were obtained in thirty minutes and in one hour, in agreement with previous results.[4] The amounts of urinary bismuth found in 4 cats receiving sobisminol solution were 0.08, 0.04, 1.2 and 1.2 mg. per hundred cubic centimeters, which indicated a rather rapid and considerable absorption of bismuth.

3. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Clinical Excretion of Bismuth After Oral Administration of Sobisminol, Arch. Dermat. & Syph. **36**:708 (Oct.) 1937.

4. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Gastrointestinal Administration of Sobisminol: Absorption, Distribution and Excretion of Bismuth, J. Pharmacol. & Exper. Therap. **62**:54, 1938. Hanzlik, Lehman and Richardson.[1]

TOXICITY

Miller's product was administered gastrically to adult white rats in excessive doses. The administration was made with a suitable small metal tube attached to a syringe. The product caused some initial, though fleeting, depression, and all the 32 rats tested recovered completely. The doses given to 12 rats of a 3 per cent solution of Miller's product were 0.5 and 0.75 Gm. of bismuth per kilogram, and of a 10 per cent solution, from 0.5 to 1.5 Gm. of bismuth per kilogram. This lack of toxicity of Miller's product was in complete contrast to the positive toxicity of sobisminol solution, of which the 100 per cent fatal dose is 0.5 Gm. of bismuth per kilogram in rats.[5] However, the absence of intestinal absorption of Miller's product in cats agreed with that of sobisminol.

COMMENT

These interesting biologic differences between the solution of Miller's bismuth compound and sobisminol solution were revealed only by a difference in choice of vehicle for the chemical reaction between sodium bismuthate (or bismuth hydroxide) and triisopropanolamine. The difference could not be due to the slight excess of triisopropanolamine in sobisminol solution, because a great excess of this amine used in preparing Miller's compound in solution did not promote gastrointestinal absorption.

The outstanding physical differences between the two products are color and stability, sobisminol solution being high and Miller's compound low. Oxidation, due to the action of sodium bismuthate, occurs in the preparation of sobisminol mass. One evidence of this is the presence of polymerized aldehydes, which may be responsible for the deep color of sobisminol solution. But whether or how these oxidation products might promote absorption is not known. Certainly, a determination of the chemical nature of sobisminol mass is desirable, as this might explain the mechanism of its gastrointestinal absorption. For the difference in procedure for chemical synthesis of sobisminol mass and of Miller's compound, small as it appears offhand, determines the practical usefulness for sobisminol mass on the one hand, and the lack of it for Miller's product, on the other, in oral antisyphilitic treatment.

The determination of the fundamental aspects of sobisminol mass appear all the more important because at present it is the only useful compound of bismuth for oral use. The following substances, which have been tried, are inadequately or not at all absorbed and lack antisyphilitic actions: bismutrate (presumably a sodium bismuthyl citrate–protein

5. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sobisminol: Toxicity, Tolerance and Irritation According to Different Channels of Administration, J. Pharmacol. & Exper. Therap. **62**:372, 1938.

complex), sodium bismuth citrate and sodium bismuth tartrate [6] and two bismuth and iodine preparations, bismuth-iodine compound (Massengill) and bisiodide (Salb).[7] When occasional traces of absorbed bismuth have been reported, as with bismutrate, sodium bismuth citrate and sodium bismuth tartrate, alkalinity is a common property, although hydrolysis and precipitation of these compounds are not completely prevented in vitro. Practically complete hydrolysis and precipitation explain the lack of absorption of the iodobismuthite complexes. Certainly, no bismuth product to date satisfies the in vitro criteria as does sobisminol mass or the correlation of these with gastrointestinal absorption of bismuth. A determination of the fundamentals of bismuth products in general may be expected to reveal reasons for differences in their actions and their utility as antisyphilitic agents.

SUMMARY AND CONCLUSIONS

Tests of gastrointestinal absorption and toxicity of solutions of a new compound of bismuth identical in chemical origin with sobisminol mass showed no demonstrable absorption of bismuth, while tests of sobisminol solution gave positive results.

Differences in physical and chemical properties between the new compound and sobisminol mass failed to satisfy certain in vitro criteria for absorption and therefore agreed with the results of tests in animals.

This lack of correlation is true for a number of other bismuth products which have failed as antisyphilitic agents, thus leaving sobisminol mass the only orally useful bismuth compound at present.

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6. Sollmann, T.; Cole, H. N., and Henderson, K.: Clinical Excretion of Bismuth: Excretion of Sobisminol and of Some Other Bismuth Preparations for Oral Administration, Arch. Dermat. & Syph. **37**:993 (June) 1938.

7. Hanzlik, P. J.: Proprietary Bismuth-Iodine Products for Oral Use in Antisyphilitic Treatment, J. A. M. A. **110**:387 (Jan. 29) 1938.

THE EARLY HISTORY OF AMERICAN DERMATOLOGY

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Scientific dermatology began on Nov. 27, 1801, when the old Hôpital Saint-Louis, in Paris, was officially dedicated to the treatment of cutaneous diseases, with Jean Louis Alibert at its head. It was Alibert and later teachers, such as Beitt, Cazenave, Devergie and Bazin, who were responsible for directing the first faltering steps of American physicians toward the light of dermatologic learning. Barely one hundred years later dermatology in America has attained a commanding position in the entire medical world; it has been given professorships in practically all of the medical colleges, has an independent department—often the largest from the point of view of floor space and attendance—in the leading hospitals, with a number of hospitals completely self contained in all allied branches devoted entirely to dermatology, and has two dermatologic journals, one covering the entire dermatologic field and the other limited to dermatologic research. Up to October 1940 in dermatology alone there were four national bodies with an enthusiastic and active membership, six sectional societies, eleven state and twenty local societies. The city of New York alone supports six of these. Is all this superlative progress dependent entirely on the activity of recent years? In my opinion, decidedly no. The real reason for the present success is largely the enormous amount of groundwork done by a small band of devoted, tireless pioneers in their chosen field of medicine. It was they who plodded through the tangled skeins of dermatologic symptomatology and classification, depending entirely on exhaustive clinical notes, unusually trained analytic and photographic minds and the development of what might be called sight diagnosis but what I sometimes call the sixth dermatologic sense. All of this developed a diagnostic acumen which greatly compensated them for their lack of present day laboratory facilities, which are unfortunately depended on to such an extent by fledgling dermatologists of today as to atrophy the very qualities of acuity of vision which made early dermatologists so eminent.

Presented as a part of an exhibit of memorabilia of early American dermatologists at the scientific exhibit of the Section on Dermatology and Syphilology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 2-6, 1941.

American dermatology may be said to have begun in New York on June 22, 1836, when the Broome Street Infirmary for Diseases of the Skin was opened under the direction of Henry Daggett Bulkley. One year later he instituted a series of lectures on cutaneous diseases at the Broome Street Infirmary, and he continued these lectures during the next three years at the Broome Street School of Medicine, at the New York Dispensary and later at the College of Physicians and Surgeons, then located in Crosby Street, delivering nine courses of lectures here during the following ten years. Bulkley was therefore not only the first to lecture on dermatology in America but the first to practice the specialty exclusively in America.

He was born in New Haven, Conn., on April 4, 1804. He received an academic degree from Yale College in 1821. He studied medicine at Yale and graduated in 1830. After graduation he went to Paris, in 1831, where he became the first American dermatologic student under Biett and Cazenave, at the old Hôpital Saint-Louis. He translated into English the "Manual of Diseases of the Skin," by Cazenave and Schedel in 1845 and in 1851 edited an American edition of Gregory's "Eruptive Fevers." At different times he was president of the New York Academy of Medicine and the New York county and New York state medical societies. It was at his home, at 42 East Twenty-Second Street, that the New York Dermatological Society was founded, and he was its first president. He died of pneumonia on Jan. 4, 1872, in his sixty-eighth year.

The second milestone in American dermatology was the publication of the first complete textbook on diseases of the skin in America, entitled "A Synopsis of the Symptoms, Diagnosis and Treatment of the More Common and Important Diseases of the Skin with Sixty Colored Figures,"[1] by Noah Worcester (1812-1847). The author was an extraordinary man, and his accomplishments in medicine were also extraordinary. His span of life was limited to thirty-five years. In that short space of time he received an A.B. degree from Harvard (1832) and an M.D. degree from Dartmouth (1838), and in 1841, after practicing medicine successfully in Cincinnati, he went to Europe in order to perfect himself in pathology and in the new art of physical diagnosis just introduced by Laennec. Part of the time spent in Paris was devoted to the study of dermatology at the Hôpital Saint-Louis. In the first year after his return to America he was elected professor of physical diagnosis and pathology of the Medical College of Ohio. In the following year (1843) the medical department of Western Reserve

1. Worcester, N.: A Synopsis of the Symptoms, Diagnosis, and Treatment of the More Common and Important Diseases of the Skin, Philadelphia, T. Cowperthwait & Co., 1845.

College at Cleveland was founded, and he was called to the chair of general pathology, physical diagnosis and diseases of the skin. He held this position until his death, giving a course in diseases of the skin for four successive years. Despite his teaching in Cleveland, he kept up his practice in Cincinnati. About this time his wife acquired tuberculosis and died. He evidently contracted the disease from her, for shortly after her death he showed the characteristic symptoms of the disease and died of it in Cincinnati, on April 4, 1847. He wrote his textbook while he was ill with tuberculosis. His contemporaries considered him a leader in pathology and the best trained man in percussion and auscultation in America.

Worcester's book is an excellent textbook, showing expert knowledge of dermatology. The diseases are clearly and graphically described, giving evidence of the definite quality of the author's scientific approach and familiarity with his subject. The sixty colored illustrations compare favorably with those in any contemporary European work.

Worcester was a contemporary of Bulkley, and these two men were a half-century ahead of their times, as no event of any importance in American dermatology occurred before 1869, when, on May 18, the New York Dermatological Society was founded at Bulkley's home through the efforts of Faneuil D. Weisse, Henry D. Bulkley, Henry G. Piffard and Foster Swift. This society is the oldest in the world, and it has been continuously active for seventy-two years. On its roster may be found the names of many of the physicians who did so much to advance the specialty of dermatology not only in New York but throughout America.

The American Journal of Syphilography and Dermatology, edited by M. H. Henry, made its appearance in 1870, with a subsequent tremendous increase in dermatologic activity throughout the country. Events occurred with startling rapidity. Scarcely a year went by without some major dermatologic event. James C. White was made the head of the newly created department for cutaneous diseases at the Massachusetts General Hospital in 1870. In 1871 he was given the first chair in dermatology to be established in America. In 1876 Piffard published his book,[2] the second textbook on diseases of the skin published in America and by no means elementary, as the modest title suggested. It was a masterly treatise, giving a complete summation of the dermatologic views up to that time interspersed with Piffard's own valuable opinions. In 1876 the first part of Duhring's "atlas" [3] appeared.

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2. Piffard, H. G.: An Elementary Treatise on Diseases of the Skin, for the Use of Students and Practitioners, New York, Macmillan & Co., 1876.

3. Duhring, L. A.: Atlas of Skin Diseases, Philadelphia, J. B. Lippincott & Co., 1876-1880, pts. 1-8.

The subsequent eight parts were published at intervals of from six to eight months. The entire work contained thirty-six chromolithographic plates by the artist Faber. These are beautifully executed and completely lack the frequent grotesque exaggeration of the colored plates of the period.

At an informal meeting held in Philadelphia on June 7, 1876, in the rooms of the Section of Practical Medicine of the American Medical Association, George H. Fox and L. D. Bulkley, of New York, Louis A. Duhring, of Philadelphia, Lunsford P. Yandell Jr., of Louisville, Ky., Edward Wigglesworth, of Boston, and J. E. Atkinson, of Baltimore, discussed the feasibility of establishing a national dermatologic society. It was decided that a meeting for organization be held in the University of Pennsylvania, Philadelphia, on Wednesday, Sept. 6, 1876, at 6 p. m. A letter to that effect was mailed to about fifty physicians interested in dermatology in various parts of the United States. Twenty-three of them responded, and these together with the six signers of the call comprised the twenty-nine original members of the American Dermatological Association. The following physicians were present at the organization: J. E. Atkinson, Baltimore; T. R. Brown, Baltimore; L. D. Bulkley, New York; S. C. Busey, Washington, D. C.; Louis A. Duhring, Philadelphia; C. Heitzman, New York; E. L. Keyes, New York; J. A. Octerlony, Louisville, Ky.; H. G. Piffard, New York; R. W. Taylor, New York; Arthur van Harlingen, Philadelphia; F. D. Weisse, New York, and James C. White and Edward Wigglesworth, Boston. A constitution and by-laws were adopted, and the American Dermatological Association was declared organized. Its first officers were: James C. White, Boston, president; Louis A. Duhring, Philadelphia, and R. W. Taylor, New York, vice presidents; L. D. Bulkley, New York, secretary, and James N. Hyde, Chicago, treasurer. The first meeting was held in Niagara Falls, N. Y., Sept. 4, 1877 and was attended by the following physicians: Atkinson, Baltimore; Brodie, Detroit; Bulkley, New York; Campbell, New York; Duhring, Philadelphia; G. H. Fox, New York; Hardaway, St. Louis; Heitzman, New York; Hyde, Chicago; Taylor, New York; van Harlingen, Philadelphia; White, Boston; Wigglesworth, Boston, and Yandell, Louisville, Ky. Thus began an organization whose influence has been of incalculable benefit to American dermatology. Since this small beginning its sphere of usefulness has increased, and its annual meetings are the most important event in dermatologic progress in America.

In 1877 Duhring published "A Practical Treatise on Diseases of the Skin," [4] dedicated to his old master, Ferdinand Hebra. The book was

4. Duhring, L. A.: A Practical Treatise on Diseases of the Skin, Philadelphia, J. B. Lippincott & Co., 1877.

carefully prepared. Its text is clear and simple; its diction is scholarly, and the definition and exposition of the varied dermatoses are comprehensive and presented in a remarkably interesting manner. With this book Duhring established himself as a leader in dermatology. The work was enthusiastically received. It went through three editions and was translated into French, Italian and Russian, a rare and almost unheard of honor for an American at that time. Duhring then had scarcely reached the age of 32.

In 1881 Piffard published "A Treatise on the Materia Medica and Therapeutics of the Skin." [5] It is an excellent work with a masterly introduction to each of the two parts, but Piffard devoted more than half the chapters to symptomatology, diagnosis and etiology, an irrelevancy common to all books published on the treatment of diseases of the skin, not only in 1881 but also in 1940. I hope that some day a book on dermatotherapy will appear which is devoted to that subject alone, a subject which is certainly large enough to fill a good-sized volume.

The year 1879 marked an epoch in the illustration of cutaneous diseases, when George Henry Fox published his "Photographic Illustrations of Skin Diseases," [6] the first attempt to illustrate dermatoses by means of photography. Between 1884 and 1891 Duhring wrote his famous series of papers, about eighteen in all, on dermatitis herpetiformis (Duhring's disease), which was an invaluable service, for it clarified a disease which had hitherto been described under such a mixed symptomatology and nomenclature that it was confusing. The papers were so clear and concise that they overcame the arguments of the opposition, led by Kaposi, and the disease has long since been established as a clinical entity. A textbook by James N. Hyde [7] was published in 1883, and was so excellent, complete and deservedly popular that in eighteen years it went through six editions. The sixth edition (1901) bears the name of Hyde's friend and associate Frank Hugh Montgomery. "Hyde and Montgomery" remained a dermatologic "best seller" for many years.

L. Duncan Bulkley's "Compendium of Diseases of the Skin," largely the result of his extensive observations in hospital and private practice, ran through approximately five editions. It first appeared in 1882.[8] It was highly individualistic, representing his personal views. In 1894

5. Piffard, H. G.: A Treatise on the Materia Medica and Therapeutics of the Skin, New York, William Wood & Company, 1881.

6. Fox, G. H.: Photographic Illustrations of Skin Diseases, New York, E. B. Treat, 1879.

7. Hyde, J. N.: A Practical Treatise on Diseases of the Skin, for the Use of Students and Practitioners, Philadelphia, H. C. Lea's Son & Co., 1883.

8. Bulkley, L. D.: Manual of Diseases of the Skin, New York, G. P. Putnam's Sons, 1882.

his treatise on "Syphilis in the Innocent" [9] appeared and won for its author the Alvarenga Prize awarded by the College of Physicians of Philadelphia in 1891. Arthur van Harlingen, an associate of Duhring for many years, published a "Handbook of the Diagnosis and Treatment of Skin Diseases" in 1884.[10] The third edition (1895) contains some extremely useful tables on the differential diagnoses of the commoner dermatoses. They are still of value for present day teaching.

James C. White called the attention of the dermatologic world for the first time to the fact that external irritants, such as plants, caused a dermatitis. His epochal work,[11] "Dermatitis Venenata, an Account of the Action of External Irritants on the Skin," was published in 1887. "A Clinical Atlas of Venereal and Skin Diseases," [12] by Robert W. Taylor, was published in 1889. This is a large folio containing fifty-eight colored plates, of by no means the excellence of those found in Duhring's atlas, but the text is very well written. Despite the unfortunate union of genitourinary diseases and dermatologic diseases so prevalent in Taylor's day, a little more than half of the atlas is devoted to dermatology.

In a bibliography of early American dermatology, 1900 should be the closing period, yet the temptation is too great and mention must be made of Stelwagon's magnum opus, his justly celebrated treatise on diseases of the skin [13] (1902), and Pusey's "Principles and Practice of Dermatology" [14] (1907). With these expositions of the viewpoint of American dermatology, this bibliography ends.

Dermatologic teaching positions in the various medical schools and the foundation of separate dermatologic departments in leading hospitals went on apace.

A great factor in the progress of American dermatology was the founding on April 8, 1882 of the New York Skin and Cancer Hospital. A brief history of the early years of this institution follows:

On April 8, 1882 the first institution in America devoted entirely to the care of cutaneous diseases and cancer first saw the light of day. On that memorable occasion a number of distinguished laymen, under the

9. Bulkley, L. D.: Syphilis in the Innocent, New York, G. P. Putnam's Sons, 1882.

10. Van Harlingen, A.: Handbook of the Diagnosis and Treatment of Skin Diseases, Philadelphia, P. Blakiston, Son & Co., 1884.

11. White, J. C.: Dermatitis Venenata, an Account of the Action of External Irritants on the Skin, Boston, Cupples & Hurd, 1887.

12. Taylor, R. W.: A Clinical Atlas of Venereal and Skin Diseases, Philadelphia, Lea Brothers & Co., 1889.

13. Stelwagon, W.: Treatise on Diseases of the Skin, for the Use of Advanced Students and Practitioners, Philadelphia, W. B. Saunders Company, 1902.

14. Pusey, W. A.: The Principles and Practice of Dermatology, New York, D. Appleton and Company, 1907.

leadership of L. D. Bulkley, gathered in a lawyer's office and associated themselves to form a society with the following objects in view: (1) the treatment of diseases of the skin and cancer by all known medical and surgical methods; (2) the study of the etiology and pathology of cancer; (3) the study of cancer with a view to its medical treatment, and (4) the reception and care of patients with chronic cancer. This society was to be known as the New York Skin and Cancer Hospital. The certificate of incorporation was filed on Nov. 11, 1882, and on Jan. 1, 1883 a small private house, at 243 East Thirty-Fourth Street, was purchased for use as a dispensary and hospital for patients with cutaneous diseases and cancer. The lower floor of this building was occupied on January 11 as a dispensary. On February 24 a small back room on the first floor was opened as a ward, with five beds. The first ward patient was admitted on February 26. The upper floors were used for hospital purposes beginning June 2, and on that date twenty-nine beds were installed.

An outstanding member of the group which founded the hospital and the one most responsible for its existence was L. D. Bulkley, as it was he who conceived the original idea. J. Francis Aitken was the hospital's first house physician, serving from Dec. 1, 1883 to Dec. 1, 1884. He joined the medical staff immediately on the completion of his internship and served continuously until his death, on Aug. 3, 1930. For forty-four years he attended the hospital three days a week. During the twenty years that I served with him he never failed to be present the minute the clinic was opened; he rarely if ever missed a day, despite bad weather and no matter how badly he might have felt at times. Aitken was a master clinician and an expert in "sight diagnosis." He always remained free from hospital politics, and when he did take sides it was always for the oppressed one. He had a great and kindly heart; he loved life, his specialty and his fellowmen.

George Henry Fox served the hospital from 1883 to 1913 and also gave it of his best, which is no faint praise to any one fortunate enough to have known Fox and his splendid career, which began seventy years ago. In that interval Fox received every possible dermatologic honor, the enumeration of which would in itself make a long article. There is no question that the successful passage of the difficult early years of the hospital was due in large part to the devotion and self sacrifice of Fox, Bulkley and Aitken. Other medical officers of the hospital in its first year were Daniel Lewis, W. T. Alexander, Robert F. Weir and Edward L. Keyes. Among the consultants were such famous physicians as W. H. Draper, Fordyce Barker, T. Gaillard Thomas, E. G. Janeway, Alfred L. Loomis and Abraham Jacobi.

Postgraduate instruction in dermatology probably began in New York in 1875 at New York University Medical College, as that great

dermatologic pioneer, Henry G. Piffard, was a member of a postgraduate faculty at that college, granting certificates to physicians completing the course. This faculty, owing to disagreements with the University, resigned on April 4, 1882 and helped found the New York Post-Graduate Medical School and Hospital on Nov. 6, 1882. The department of dermatology and syphilology of the New York Post-Graduate Medical School and Hospital at its inception was a part of the department of genitourinary and venereal diseases, under the leadership of Frederick R. Sturgis, and it was established at the same time as the school. As Sturgis' time was completely taken up with the teaching of genitourinary diseases, it is logical to suppose that Piffard took up the teaching of cutaneous diseases; this supposition is further strengthened by the fact that he was a member of the original postgraduate faculty at New York University in 1875 and an active leader in the secession of this faculty from the university in 1882. He was on the first list of professors of the New York Post-Graduate Medical School and Hospital when it was founded, and, as far as I can ascertain, he limited his work entirely to dermatology.

It is interesting to note that as early as 1889 the New York Post-Graduate Medical School and Hospital recognized the advisability of full time instruction in dermatology and the separation of this subject from genitourinary diseases. A separate dermatologic department was at long last organized, with George Henry Fox as professor, G. T. Jackson and F. B. Carpenter as instructors and C. W. Cutler and F. J. Leviseur as clinical assistants. Thus was launched on its enviable career a great factor in postgraduate instruction in dermatology in America.

George Henry Fox, the head of the new department, had already gained a high reputation in his specialty. He was at the head of his own service at the New York Skin and Cancer Hospital and was also professor of dermatology at the College of Physicians and Surgeons. Fox died on May 3, 1937, in his ninety-first year, and in his long span of life he had received a host of dermatologic honors. Besides his great friendliness, sociability and joviality, he had another but much rarer attribute, namely, modesty. After he had spent some years as professor and vice president at the New York Post-Graduate Medical School and Hospital, a serious disagreement arose as to the management of its affairs, and he resigned. He was succeeded by Robert W. Taylor, one of the organizers of both the New York Dermatological Society and the American Dermatological Association. Taylor was such an avid reader of current literature that he could not only cite authors but give their opinions verbatim. He had a remarkable memory and could frequently relate years later clinical histories of patients, even recalling their names. In discussions he was fond of high-sounding names and particularly

liked the word "epiphenomenon." Because of his extraordinary memory and complete knowledge of the current literature, he must have made a splendid teacher.

George T. Elliot was next in line as head of the department. He deserved the honor, as he had served as an assistant from the inception of the service under Professor Sturgis. He later became professor of dermatology and syphilology at Cornell University and from 1882 to 1901 was Bulkley's chief of clinic at the New York Skin and Cancer Hospital. Charles W. Allen (1854 to 1906) also served as professor of dermatology. He devoted much attention to roentgenotherapy and phototherapy and paved much of the way for others in those respective fields. He was jovial and had an overflowing good humor. He died prematurely at Gibralter while on his way home from the Fifth International Dermatological Congress at Lisbon, Portugal, to which he was a delegate from the American Dermatological Association. Sigmund Pollitzer served the school as professor of its department of dermatology from 1895 to 1915.

It may be well at this time to give some "thumb nail" sketches of a few of the men who changed a dermatologic wilderness into a fertile field. We have already given data in reference to the first two men, Henry Daggett Bulkley and Noah Worcester. For the rest, no attempt will be made at chronologic order.

JAMES CLARKE WHITE (1833-1916)

James Clarke White, one of the outstanding pioneers in American dermatology, was born on July 7, 1833. After a distinguished career as a student at America's oldest university, Harvard, from which he graduated in 1853, he spent a year abroad under the tutelage of that master dermatologist and brilliant teacher, Ferdinand Hebra. On his return to Boston in 1857, he took up general practice but never missed an opportunity to widen his dermatologic experience. In 1860 he opened a dispensary for cutaneous diseases. In 1863 he was appointed as lecturer on diseases of the skin at Harvard Medical School. The Massachusetts General Hospital created a department for diseases of the skin in 1870, and White was, naturally, their logical choice for head of the department. He served this institution devotedly for thirty-three years. In 1871 he had the signal and deserved honor of being awarded the first chair in dermatology to be established in the United States. Both these events marked a turning point in his career. He now gave up his general practice and began the life work in which he was to accomplish so much. Between 1856 and 1913 White contributed to dermatologic literature approximately one hundred and twenty-five articles, fifty reviews, ninety-four editorials, twelve addresses and eight

books and chapters. In June 1889 an article entitled "A Case of Keratosis (Ichthyosis) Follicularis" [15] appeared. White instead of Darier should have had the disease named after him, because Darier's article did not appear until a few months later. On May 14, 1887 White published a 210 page book [11] on dermatitis venenata, which was the first presentation of this important subject in dermatologic literature. He served as chairman of the Section of Dermatology and Syphilology of the International Medical Congress held in Philadelphia on Sept. 4 to 9, 1876. He became the first president of the American Dermatological Association, in 1877. Twenty-one years later he was again elected president of that distinguished body. In 1907 he was made president of the Sixth International Dermatological Congress, which was held in New York. White became a corresponding member of the French and Argentine dermatologic societies and an honorary member of the Italian, London, Vienna, Berlin and New York dermatologic societies.

White was dignified in appearance and somewhat austere in manner, especially when conducting scientific sessions. Away from the rostrum he was courteous and pleasant. He had a full and busy life. He knew how to work and how to play. With abundant health, fame, a splendid family, ample means, a devoted wife and such hobbies as botany, natural history, porcelains and colonial furniture, he was indeed a happy man. He even lived long enough to witness the enormous progress of his beloved specialty.

HENRY GRANGER PIFFARD (1842-1910)

Henry G. Piffard played an important role in the development of American dermatology. Through his brilliant, many-faceted mind, bordering on genius, he focused the attention of America, if not of Europe, on his specialty, which during his early years was still in its infancy; its growth to lusty manhood was due in part to his devoted ministrations.

Piffard was born in Piffard, N. Y., on Sept. 10, 1842. He graduated from the University of the City of New York in 1862 and received his medical degree from Columbia University College of Physicians and Surgeons in 1864. His interest in dermatology manifested itself soon after graduation. He left for Europe to perfect himself in the specialty and visited various medical centers but spent most of his time with Tilbury Fox, at the latter's dermatologic clinic at the University College Hospital in London. It was there that his lifelong friend, George Henry Fox, first met him. The close friendship uniting them lasted until Piffard's death, nearly forty years later. The friendly association of these two men for nearly half a century can readily be understood by

15. White, J. C.: A Case of Keratosis (Ichthyosis) Follicularis, J. Cutan. & Genito-Urin. Dis. **7**:201, 1889.

those fortunate enough to be familiar with them and to know how much they accomplished in establishing a firm foundation for the specialty they both loved, not only in the city of New York but in the world at large.

Piffard on his return from Europe established himself in New York. He helped materially in the founding of the New York Dermatological Society, on May 18, 1869. This medical body has the honor of being the oldest dermatologic society in the world. Piffard was also one of the organizers of the American Dermatological Association and later its president. In 1871 he became visiting dermatologist to the New York City Hospital (Welfare Island), the first institution in the United States to establish dermatologic wards. He served this institution until 1885, when he was appointed consulting dermatologist. He became professor of diseases of the skin in the medical department of New York University in 1874 and served this institution for many years. He was its emeritus professor at the time of his death.

Piffard wrote the second original textbook on diseases of the skin [2] to be published in America, but as early as 1868 he had translated Hardy's "The Dartrous Diathesis, or Eczema and its Allied Affections." In 1881 his "Treatise on Materia Medica and Therapeutics of the Skin" [5] first appeared. According to Andrew R. Robinson, Piffard deserves the credit for the first use of the term tuberculid, as he described such a lesion in 1892, four years before Darier's work on the subject.

Piffard had a warm heart, and though he was most combative at times, even to the point of eccentricity, he was a lover of peace and good will. As George Henry Fox aptly put it, he was "a blazing meteor in our dermatologic firmament."

HENRY WEIGHTMAN STELWAGON (1853-1919)

Henry W. Stelwagon had the rare quality of inculcating among those with whom he came in contact a deep affection for him and a high regard for his extraordinary dermatologic ability as a writer, clinician and teacher. If his fame depended on his textbook alone, this in itself would be sufficient to make him immortal.

Stelwagon was born in Philadelphia on Dec. 3, 1853. He received the degree of B.S. from Andalusia College in 1872, and the degrees of Ph.D. and M.D. from the University of Pennsylvania in 1875. After an internship in the Philadelphia General Hospital, he went abroad to study his chosen specialty at the two great dermatologic centers, Vienna and Berlin, then at the height of their fame. He spent two full years in assiduous work under the great masters of that time.

His first dermatologic appointment on his return to Philadelphia came from the Northern Dispensary, as chief physician in its department of

cutaneous diseases. Probably through sentimental reasons, he retained his connection with this institution throughout his life, despite more important appointments received later on in his distinguished career. In 1880 the first test of his mettle came through his appointment as successor to Duhring at the Philadelphia Dispensary for Skin Diseases. This institution had been organized by Duhring in 1870. Stelwagon kept this appointment for ten years and in that time proved himself a worthy successor to his great preceptor. In 1885 he became instructor in dermatology in the University of Pennsylvania and chief of the dispensary for cutaneous diseases of the University Hospital. At this time he did practically all of the teaching, owing to the ill health of Professor Duhring. In 1888 he was elected clinical professor of dermatology in the Women's Medical College of Pennsylvania and was appointed dermatologist to the Philadelphia General Hospital. In 1890 he resigned from the University of Pennsylvania School of Medicine and soon thereafter was elected professor of dermatology at the Jefferson Medical College of Philadelphia, where he continued to teach until ill health compelled his resignation in June 1918.

Stelwagon contributed to various medical journals throughout his years of active life many valued dermatologic articles. He also wrote many chapters on cutaneous medicine for at least a dozen encyclopedic works. In 1890 he published a small book [16] for the use of students. It was arranged in quiz-compendium form and, though condensed, was extremely accurate and an invaluable aid to the student. It went through innumerable editions and in my opinion did more to push dermatologically lazy students through a successful examination than any other single agent. Stelwagon's magnum opus [13] first appeared in 1902, with a dedication to that master dermatologist Duhring, and immediately assumed its rightful position as the authoritative American textbook on cutaneous medicine. By careful and frequent revision, Stelwagon maintained for nearly twenty years the preeminence of the book. In the spring of 1919 he began the ninth edition, but ill health forced him to relinquish it to Henry K. Gaskill, who carried it on to completion. Stelwagon was an honorary or corresponding member of many foreign dermatologic societies. He died of angina pectoris, on Oct. 18, 1919. Milton B. Hartzell, intimately associated with him for many years, stated that he "had never heard him say an unkind word to or about anyone. . . . He was indeed a gentleman. . . . Those who knew him best loved him most." In speaking of Stelwagon in this manner, Hartzell only voiced the opinion of most of his acquaintances.

16. Stelwagon, H. W.: Essentials of Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1890.

SIGMUND POLLITZER (1859-1937)

Sigmund Pollitzer was an outstanding figure in the dermatologic world. He graduated from Columbia University College of Physicians and Surgeons in 1884. After graduation he left for Europe and undertook research work in physiology in Heidelberg, Germany, and in bacteriology in Fresenius' laboratory in Weisbaden, Germany; later he took up special work in Virchow's laboratory and at this time did much original work in physiologic chemistry. It was not until 1889 that he entered on his life's work, first at Unna's clinic and then as an assistant to Sir Malcom Morris, in which position for a time he edited the *British Journal of Dermatology* under Morris' direction. From London he went to Paris, and there began a lifelong friendship with Darier, whose textbook he translated into English in 1920. Pollitzer made approximately seventy-one contributions to dermatologic literature. Among the best remembered are his monographs on acanthosis nigricans, xanthoma of the eyelid, hydradenitis suppurativa, parakeratosis variegata, arsphenamine for the treatment of syphilis and serum therapy and serologic diagnosis in syphilis. Pollitzer was an expert histopathologist. He was a strict parliamentarian and was especially critical of long-winded discussions lacking concrete facts. In such instances he could in a few words of polished English and in well chosen scientific terms completely smother the unhappy speaker with unassailable facts, from which there was nothing else to do than to retire in confusion. Pollitzer in acting thus did much good service, for he deflated the ego of the usual group of know-it-alls who frequent every dermatologic meeting. In his home and with his friends he exuded kindness, generosity and simplicity. Pollitzer was professor of the department of dermatology of the New York Post-Graduate Medical School and Hospital from 1895 to 1915. Despite his honors and his high ability, he was always the earnest student. He belongs to that small group of physicians who have placed dermatology on a sound, dignified and scientific basis. I have always considered the friendship that Pollitzer evinced for me as one of the great satisfactions of my life.

LOUIS ADOLPHUS DUHRING (1845-1913)

Philadelphia produced in the person of Louis Adolphus Duhring a master in dermatology. After graduating from the University of Pennsylvania in 1867 and serving an internship in the Philadelphia Hospital, he went abroad and devoted himself assiduously to the study of dermatology in Vienna, under Hebra, and also in Berlin, London and Paris. His vacation periods were spent in the study of leprosy in Constantinople and in Norway. He was one of the founders of the American Dermatological Association and twice its president. In 1877 he published the third American textbook on cutaneous diseases, which ran through three

large editions. He also brought out a chromolithographic atlas on cutaneous diseases and projected an encyclopedic work on diseases of the skin to be issued in parts.[17] The first part appeared in 1895 and the second in 1898, but the work was never completed. He was a prolific writer, a score of articles being on the subject of dermatitis herpetiformis, which disease bears his name.

Duhring soon received the appointment of clinical lecturer at the University of Pensylvania; he then advanced to the position of clinical professor and later to that of full professor, a post which he filled with great honor from 1875 to 1910. Duhring was a great teacher and a clear, comprehensive and accurate writer. His descriptions of dermatitis herpetiformis are masterly in form and clarity. In his clinical work he was never satisfied until he had gone over a completely stripped patient from head to foot. In his later years he became much less active and devoted much time to financial speculation. When he died, on May 8, 1913, he left, to every one's astonishment, more than a million dollars, which, after generously providing for relatives, he devoted to his alma mater, medical societies and charities. His most faithful associate was Arthur van Harlingen, of Philadelphia.

ARTHUR VAN HARLINGEN (1845-1936)

Duhring's associate, Arthur van Harlingen, of Philadelphia, was also a founder of the American Dermatological Association. He was a fellow intern of Duhring's at the Philadelphia Hospital in 1867 and assisted him in the dispensary and outpatient department of the University Hospital. He helped found the Philadelphia Polyclinic in 1885 and became its first professor of dermatology. He illustrated with pen and ink drawings the second edition of Duhring's "Treatise on Skin Diseases" and published a handbook[10] on cutaneous diseases which ran through a number of editions. This book contains tables of the differential diagnosis of the commoner dermatoses, which are of great practical value.

SAMUEL SHERWELL (1841-1928)

Samuel Sherwell, of Brooklyn, was a pioneer in dermatology in that borough. He studied abroad under Hebra, joined the Anglo-American Ambulance Corps with Dr. Marion Sims and Sir William McCormack during the Franco-Prussian War and received from the Bavarian government the military order "pour le mérite."

Sherwell returned to Brooklyn in 1871. In 1877 he was appointed lecturer on diseases of the skin at the Long Island College Hospital, and later he became its first professor of this subject. He served this institution faithfully for thirty years. He was president of the New York

17. Duhring, L. A.: Cutaneous Medicine: A Systematic Treatise of the Diseases of the Skin, Philadelphia, J. B. Lippincott Company, 1895, pt. 1; 1898, pt. 2.

Dermatological Society twice and of the American Dermatological Association once. Sherwell lived long and interestingly. His "Recollections of an Old Boy" [18] makes fascinating reading. He was particularly fond of the New York Dermatological Society, in which he was elected to active membership in 1873 and to honorary membership in 1920.

WILLIAM H. DRAPER (1830-1901)

William H. Draper, of New York, was a charter member of the New York Dermatological Society and at that time a professor of diseases of the skin at Columbia University College of Physicians and Surgeons. He was well versed in his specialty but was also interested in general medicine.

FANEUIL D. WEISSE (1842-1915)

Faneuil D. Weisse, of New York, was a student under Erasmus Wilson. He was practically the founder of the New York Dermatological Society. He wrote little on dermatology, but he was greatly interested in it and was particularly gifted in stimulating the interest of his fellow workers in the subject.

FRANK P. FOSTER (1841-1911)

Frank P. Foster, of New York, was a scholarly man. He was elected to the American Dermatological Association in 1877 and was for many years a member of the New York Dermatological Society. He also edited the *New York Medical Journal.*

GEORGE HENRY FOX (1846-1937)

George Henry Fox received his A.B. degree from the University of Rochester in 1867 and his M.D. degree from the University of Pennsylvania in 1869. He succeeded Duhring in an internship at "old Blockley" (Philadelphia) and was shown through that institution by his fellow intern Arthur van Harlingen; thus, by a strange coincidence, that institution within the space of three years nurtured three men who were destined to accomplish much in American dermatology. When his term of service expired, he left for Europe for intensive dermatologic training. In Berlin he studied under Virchow; in Vienna, under Hebra, Neumann, Schroetter and Stoerk. In Paris he was a pupil of Bazin, Hardy and Vidal, and in London, of Tilbury Fox and Jonathan Hutchinson. He worked assiduously under these great masters for three years. It was in Tilbury Fox's service at the University College Hospital that he first met a fellow countryman, from New York, Henry G. Piffard. The two men immediately became close friends, and they remained so until the death of Piffard, nearly forty years later.

18. Sherwell, S.: Recollections of an Old Boy, New York, Knickerbocker Press, 1923.

Fox settled in New York in 1873, and in the same year he was elected to membership in the New York Dermatological Society, of which organization he was elected president four times. In 1876 he was one of the six founders of the American Dermatological Association. During the year of the Golden Jubilee (1925-1926) he served as honorary president, receiving the gavel from his son, Howard Fox, the retiring president. Between the years 1875 and 1907 Fox served as professor of diseases of the skin at the Women's Medical College of the New York Infirmary, Starling Medical College, Columbus, Ohio, the New York Post-Graduate Medical School and Hospital and the College of Physicians and Surgeons, New York. He resigned from the last-mentioned institution years before the retiring age, in order that George T. Jackson, his chief assistant, might serve as professor—an example of his usual generosity to his subordinates. From 1883 to 1913 Fox was attending dermatologist at the New York Skin and Cancer Hospital.

In 1879 Fox published his "Photographic Illustrations of Skin Diseases." [6] Other editions appeared in 1881 and 1885. His "Skin Diseases of Children" [19] was published in 1897. He described matchbox dermatitis in 1888, probably the earliest report of contact dermatitis in the literature. In 1902, in collaboration with Fordyce, he reported a chronic itching papular eruption of the axillas and pubes (Fox-Fordyce disease).[20] He was elected president of the Medical Society of the County of New York in 1891 and of the Medical Society of the State of New York in 1894. In 1926 he published his "Reminiscences," [21] a delightful account of his life, every page of which evinces his extraordinary modesty. On the many occasions that we were together, I never heard him speak of his own honors, but he was always ready to speak of those around him who had attained a high degree of proficiency in the specialty he had so greatly loved. Another of Fox's most lovable traits was the extraordinary friendship and interest which he manifested for the young tyros of his specialty. His willingness to help them in every way possible was expressed without the slightest trace of condescension. As Pusey rightly stated, "He was perhaps the friend of more American dermatologists than any other one of his generation."

PRINCE A. MORROW (1846-1913)

Prince A. Morrow was born on Dec. 19, 1846, at Mount Vernon, Christian County, Ky. He received the degree of Bachelor of Arts in Kentucky in 1864 and that of Doctor of Medicine from New York University in 1873. After two years of postgraduate work in dermatology,

19. Fox, G. H.: Skin Diseases of Children, New York, William Wood & Company, 1897.

20. Fox, G. H., and Fordyce, J. A.: Two Cases of a Rare Papular Disease Affecting the Axillary Region, Tr. Am. Dermat. A. (1901), 1902, p. 83.

21. Fox, G. H.: Reminiscences, New York, Medical Life Press, 1926.

syphilology and genitourinary diseases in Europe, he located in New York, where he rapidly rose to eminence. He became professor of genitourinary diseases at New York University and Bellevue Hospital Medical College in 1883. He was also an attending physician to the department of cutaneous and venereal disease of the New York Hospital. He was a corresponding or honorary member of most of the foreign dermatologic societies, and he served as secretary of the International Congress of Dermatology and Syphilology in Paris in 1890 and in Vienna in 1893. He edited the *Journal of Cutaneous and Genito-Urinary Diseases* with Piffard from 1883 to 1888 and with Fordyce from 1888 to 1891.

Morrow gained his greatest fame in the prophylaxis of venereal diseases, devoting most of his later life to this work. He was the founder of the American Society of Sanitary and Moral Prophylaxis. He founded *"Social Diseases,"* a journal devoted to that subject. Morrow was tall, handsome and dignified almost to the point of austerity, but with his intimate friends he proved a congenital companion.

WILLIAM A. HARDAWAY (1850-1923)

William A. Hardaway was born on June 8, 1850, at Mobile, Ala. He arrived in St. Louis at the age of 7 years, and that city remained his home until his death. After receiving an academic degree from the University of Virginia, he graduated from the Missouri Medical College, in 1870. Hardaway was a founder of the American Dermatological Association and its president in 1885. He published eighty-one papers within forty years. He published a "Manual of Skin Diseases" in 1891 and in 1898.[22] He was a clear and forceful teacher during the many years he spent at the Missouri Medical College until he resigned in 1910. He was a splendid clinician, with a high diagnostic acumen, the result of his long and rich experience. He is best known because of his introduction in dermatology of the electrolytic method, in 1877. He was always most careful to give credit to Dr. Charles E. Michel, who, the year before, had recommended this method for the destruction of "wild hairs" of the lids.

ANDREW ROSE ROBINSON (1845-1924)

Andrew Rose Robinson was born on July 31, 1845, at Claude, Ontario, Canada. He graduated in medicine from Bellevue Hospital Medical College in 1868 and received the same degree a year later at the University of Toronto. He did postgraduate work in London, Paris and Vienna. He was a pioneer histopathologist, a bent developed in his work abroad. This interest in pathology led to his appointment as

22. Hardaway, W. A.: Manual of Skin Diseases, Philadelphia, Lea Brothers & Co., 1891; A Clinical Manual of Skin Diseases, ed. 2, ibid., 1898.

professor of histology and pathologic anatomy at the New York University Medical College and Women's Medical College of the New York Infirmary for Women and Children, but the institution nearest his heart was the New York Polyclinic Medical School and Hospital, of which he was one of the founders and professor of dermatology for many years. Dr. Robinson was one of the charter members of the American Dermatological Association and its president in 1896. He was the first chairman of the Section of Dermatology and Syphilology of the New York Academy of Medicine and was a member of the New York Dermatological Society for many years. His "Manual of Dermatology" appeared in 1884. He was the first to describe hidrocystoma.

L. DUNCAN BULKLEY (1845-1928)

L. Duncan Bulkley received his medical degree from Columbia University College of Physicians and Surgeons in 1869 and spent several years at the Hôpital Saint-Louis, in Paris. On his return to New York he became most active in dermatology. He was one of the founders of the American Dermatological Association and its secretary at the first annual meeting, which was held at Niagara Falls, N. Y., on Sept. 4, 1877. Dr. Bulkley founded the New York Skin and Cancer Hospital on Jan. 1, 1883 and began a series of clinical lectures there in 1899. They became quite popular, and he kept them up until a few years before his death. He wrote several hundred articles and six or eight textbooks, mostly devoted to dermatotherapy, in which he had a deep interest. Bulkley was largely responsible for the formation of the Section on Dermatology and Syphilology of the American Medical Association, in Chicago in 1888, and he was chairman of its first meeting, on May 8, 1888 in Cincinnati.

AUGUSTUS RAVOGLI (1851-1934)

Augustus Ravogli was a pioneer in dermatology in Cincinnati. He was born in Rome, Italy, on Feb. 7, 1851. He received the degree of A.M. from the Roman College in 1868 and of M.D. from the University of Rome. He did postgraduate work in Vienna, Prague and Berlin. He came to the United States in 1883 and settled in Cincinnati, where he soon became prominent in dermatology. For many years he was professor of dermatology and syphilology at the University of Cincinnati, and he was also attending and later consulting dermatologist to the Cincinnati General Hospital. Ravogli was elected a member of the American Dermatological Association in 1899 and became its president in 1916-1917. He wrote a book on the hygiene of the skin and an important one on the medicolegal and sociologic aspects of syphilis, which is now somewhat rare. He was extremely active in the early years of the Section of Dermatology and Syphilology of the American Medical Association. He was its host at its first meeting, in Cincinnati on May 8,

1888, and one of its saviors when it fell into evil days some years later. In fact, it was only when he served as chairman in 1897 that the Section experienced a renaissance.

JAMES N. HYDE (1840-1910)

James N. Hyde was in every respect the pioneer in dermatology in Chicago. He gave the first lectures on that subject there, at Rush Medical College in 1873. At this college in 1879 he was made professor of dermatology and venereal diseases, a position which he held until his death. He also taught in the Post-Graduate Medical School in Chicago. From 1902 he was professorial lecturer on dermatology at the University of Chicago. Hyde was a charter member and twice president of the American Dermatological Association. He wrote many dermatologic articles. His best known studies were on blastomycosis, sporotrichosis and pellagra. He first described synovial lesions in the skin in 1883, but he gave credit for the first demonstration of these lesions to Jones and Markin, of St. Thomas Hospital, London. Hyde's best literary effort was his book on Diseases of the Skin,[7] the first edition of which appeared in 1883 and the eighth and last in 1909. The first edition consists of 560 pages of text and the eighth of 1,100 pages, a fitting commentary on the progress of American dermatology in twenty-six years. Hyde duplicated Duhring's ability in the selection of assistants. Duhring had van Harlingen, Hartzell and Stelwagon; Hyde enlisted the services of Montgomery and Ormsby.

FRANK HUGH MONTGOMERY (1862-1908)

Frank Hugh Montgomery was born in 1862 at Fairhaven, Minn. After graduating from Rush Medical College, he undertook postgraduate work in dermatology in Paris, London and Vienna. On his return to Chicago he joined the faculty of Rush Medical College in 1890 and two years later became the office associate of James N. Hyde. Thus began a unique association founded on mutual appreciation, respect and affection. As time went on, these bonds became more binding, and at the time of Montgomery's death, Hyde practically treated him as a son. Montgomery was a hard worker. Many articles were published under the famous team name of Hyde and Montgomery, and several editions of the famous textbook appeared under the two names. Montgomery published a considerable number of articles alone, including some on blastomycosis. At the time of his death, on July 14, 1908, Montgomery was associate professor of dermatology at Rush Medical College and dermatologist to four Chicago hospitals. He was an active member of the American Dermatological Association and served as its secretary for three years and its vice president once. He was most active in the Chicago Dermatological Society and had been elected president.

Ormsby, who was long associated with Montgomery, spoke of him as follows:

> He was remarkable for his acuteness as a diagnostician, his skill as a pathologist and practitioner, and his extreme thoroughness in all that he attempted. He was a singularly modest man, sweet in disposition, clean in every act of his life, charming among his friends and greatly beloved by all who constituted his clientele.

JOSEPH ZEISLER (1858-1919)

Zeisler was born in the town of Bielitz, Austrian Silesia. He graduated in medicine from the University of Vienna in 1882, served his internship in the Vienna General Hospital and worked under Kaposi. He came to Chicago in 1884. For a short time he was professor of cutaneous and venereal diseases at the Post-Graduate Medical School. After serving for about a year, he was proffered the chair of professor of cutaneous and venereal diseases at Northwestern University, which he accepted. He served this institution with great distinction until his retirement, in 1917.

Zeisler was chairman of the Section on Dermatology of the American Medical Association in 1912, president of the American Dermatological Association in 1903 and twice president of the Chicago Dermatological Society. He wrote most ably and was a forceful public speaker. With his thorough knowledge of the classics, music and the fine arts, it could not well be otherwise.

WILLIAM ALLEN PUSEY (1865-1940)

The great cities of the United States have produced a number of physicians who became preeminent in dermatology, but none produced a more distinguished one than Chicago in the person of William Allen Pusey. He was born in Elizabethtown, Ky., on Dec. 1, 1865. His home environment there was most happy, and he evidenced this throughout the years by his frequent returns there, despite the busiest of lives. He and his brother, Dr. Brown Pusey, established the Brown-Pusey House, which is the community recreational and cultural center of Elizabethtown. He married Sallie Warfield Cunningham, of Elizabethtown, and Mrs. Pusey's devoted help throughout his life must have been an important factor in his remarkable career. I am indebted to her for her great kindness in the loan of important material relative to Dr. Pusey, including the unique hand-decorated scroll of resolutions presented to him by the Chicago Dermatological Society in 1936 at a testimonial dinner. On the back of the frame Pusey had written: "Hang in my room at B.-P. House." This and the testimony of Herbert Rattner, that he was so moved that his voice broke and his lips trembled, are sufficient evidence that of all the innumerable honors he had received, this was the superlative one.

It is an impossible task to give a "thumb nail" sketch of William Allen Pusey. The figure of the man is too colossal; one could just as well attempt to reproduce the Statue of Liberty in a small miniature painting. The man was so gifted and accomplished so much in dermatology and its history and in philosophy, general literature, editorial work and even poetry, that to record clearly what he did with his life would take a large volume. As this is impossible here, let me deal in dry facts. He graduated from Vanderbilt University in 1885 and was class valedictorian. He received his medical degree from New York University Medical College and spent two years working at the New York Skin and Cancer Hospital. Two more years were taken up in Europe at the clinics of the great teachers of Vienna, Berlin, London and Paris. He settled in Chicago in 1893. At the age of 29 he became professor of dermatology at the College of Physicians and Surgeons of Chicago. After the affiliation of this college with the University of Illinois, he continued in the same capacity until 1915. As early as 1900 he began his pioneer work with roentgen rays. His textbook on that subject appeared in 1903. In 1905 he suggested the use of solid carbon dioxide for the treatment of certain types of dermatoses. In 1907 "The Principles and Practice of Dermatology" [14] appeared. The book represented Pusey's own dermatologic experience based on his work at the Cook County Hospital, teaching and private practice, but the best of the knowledge of others was also amply utilized. It ran through four editions.

In 1923, at the Seventy-Fourth Annual Session of the American Medical Association, Pusey was elected president. It must have been a great satisfaction to him, as he had served that organization faithfully and long. He was its treasurer for eleven years and a member of its House of Delegates and had worked equally in its interest when he was just a humble member of it.

Pusey became editor of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in 1920. He immediately induced the American Medical Association to take over publication of this journal, even though it had been run at great financial loss. Under Pusey's personal editorship the ARCHIVES soon became one of the foremost dermatologic journals in the world. Three years before his death Dr. Pusey had the unique experience of receiving the evidences of the great appreciation and affection felt for him not only by those who knew him well but by others less fortunately situated yet who realized what he had accomplished for the specialty throughout a lifetime of devotion and unsparing effort. The first number of volume 35 (January 1937) of the ARCHIVES was specially dedicated to him. It contained seven articles on his varied activities and some personal reminiscences.

JOHN A. FORDYCE (1858-1925)

John A. Fordyce received an A.B. degree from Adrian College in 1878. He graduated from Northwestern University Medical School in Chicago in 1881, served as intern in the Cook County Hospital until 1883 and practiced general medicine at Hot Springs, Ark., for three years. He then went abroad for postgraduate study in dermatology. On his return to the United States, in 1888, he settled in New York. In 1889 he became associated with Prince A. Morrow in the editorship of the *Journal of Cutaneous and Genito-Urinary Diseases*. In 1892 he was sole editor. He resigned in 1897. In 1893 Fordyce was appointed professor of dermatology in the Bellevue Hospital Medical College. In 1898 New York University Medical College and Bellevue Hospital Medical College combined, and Fordyce became professor of dermatology and syphilology in the new institution, New York University College of Medicine. He kept this position until 1912, when he resigned in order to accept a similar one with Columbia University College of Physicians and Surgeons. He retained this position until his death. He also served New York City Hospital (Welfare Island) from 1893 until his death in 1925.

An enumeration of his honors and achievements would be beyond the scope of this paper; suffice it to say that he was a prolific writer, and —what is more important—of his more than a hundred monographs, many marked an advance in the specialty to which he devoted his superabundant energy. In his long career he became at different times the presiding officer of the various important dermatologic societies in America. Despite a large private practice, extensive teaching and much hospital work, he always found time to encourage and help the younger physicians, no matter how obscure. The consolidation of syphilology with dermatology in colleges and other medical organizations was greatly aided by his efforts. He was a great histopathologist, his bent in this direction having developed under the inspiration of Kaposi. Like most great men he was modest and extremely diffident.

American dermatology suffered an irreparable loss in his death, on June 4, 1925, two weeks after an appendectomy. As George M. MacKee aptly put it, "He died in harness, as would have been his wish."

EDWARD L. KEYES (1843-1924)

Edward L. Keyes was born at Fort Moultrie, in Charleston harbor, S. C., on Aug. 28, 1843. His father, an army officer, who eventually became a Major General, U. S. A., was stationed there at the time. He received his A.B. degree from Yale University in 1863 and his M.D. degree from New York University Medical College in 1866. On the advice of his preceptor, William H. Van Buren, he went abroad to

specialize in dermatology. He was one of the founders of the New York Dermatological Society in 1869 and was a charter member of the American Dermatological Association. In 1871 he was appointed lecturer in dermatology at Bellevue Hospital Medical College, and in 1881 he became professor of cutaneous and genitourinary diseases at the same school. He served the New York City Hospital (Welfare Island) from 1870 to 1876 and one year later was appointed consultant.

Keyes was deeply interested in genitourinary surgery, but he made a number of valuable contributions to dermatologic literature. One of his greatest contributions was a paper on the effect of small doses of mercury on syphilitic blood,[23] which first appeared in January 1876. This paper was incorporated in an essay on the same subject, which was read by Keyes before the Section on Dermatology and Syphilis in the International Congress, at Philadelphia in September 1876. W. H. Van Buren and E. L. Keyes collaborated in a textbook of genitourinary diseases and syphilis, which remained a classic for many years.

ROBERT W. TAYLOR (1842-1908)

Robert W. Taylor made important contributions to the study of syphilis. His book on syphilis of the bone is an important contribution to the subject, and so was his "atlas." Taylor was one of the organizers of both the New York Dermatological Society and the American Dermatological Association. He taught dermatology at the New York Post-Graduate Medical School and Hospital, succeeding George H. Fox as professor. In 1876 he described idiopathic atrophy of the extremities. Known to his intimates as "Bob" Taylor, he was a man of forceful opinions and a born fighter.

THOMAS CASPAR GILCHRIST (1862-1927)

Thomas Caspar Gilchrist was born on June 15, 1862, at Crewe, Cheshire, England. He came to the United States in 1889, and after some time spent with Duhring in Philadelphia, he settled in Baltimore in 1890. He became associated with Morrison at the Johns Hopkins Hospital, and after Morrison's death he became chief of the dermatologic department of the dispensary. In 1897 he became clinical professor of dermatology in the Johns Hopkins University School of Medicine and retained this position until his death. He also occupied the chair of dermatology at the University of Maryland. His energy and capacity for work were boundless. At one time he did considerable work in microscopy in Dr. Welch's laboratory.

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23. Keyes, E. L.: The Effect of Small Doses of Mercury in Modifying the Number of Red Blood Corpuscles in Syphilis: A Study of Blood-Counting with the Hématimètre, Am. J. M. Sc. **71**:17, 1876.

In June 1894 Gilchrist demonstrated blastomycosis for the first time, before the American Dermatological Association in Washington, D. C. Gilchrist's priority over Buschke and Busse is unquestioned. Gilchrist clearly demonstrated a characteristic clinical picture with a definite demonstration of the cause. Pusey stated:

> His description clinically and mycologically and his demonstration of the pathogenicity of the organism was so accurate and complete that little has been added to it since. It established beyond question an important new disease among the infectious granulomas.

The immense amount of work involved cannot be appreciated without a study of the original articles on blastomycosis by Gilchrist, which appeared in the Johns Hopkins Hospital reports.

JOHN T. BOWEN (1857-1940)

John T. Bowen, unlike the majority of his contemporary fellow dermatologists, was born, educated, practiced, worked and died in one city, Boston. He graduated from Harvard University in 1879 and from Harvard Medical School in 1884. From 1884 to 1887 he was in Europe doing postgraduate work. His first appointment was as assistant physician in the outpatient department for cutaneous diseases at the Massachusetts General Hospital in May 1889, with that master dermatologist James C. White as his chief. In 1895 he became physician in the same institution, where he remained until his retirement as a consultant in 1914. In 1896 he was made an instructor in dermatology at Harvard Medical School. In 1902, on the retirement of James C. White, Bowen was appointed assistant professor, and in 1907 he became professor of dermatology, serving until 1911, when he was elected professor emeritus. In 1927 he retired from practice. Bowen was a confirmed microscopist, with the result that two papers he produced [24] will always be associated with him and Bowen's disease will be a subject for discussion for years to come.

COMMENT

The exhibit presented and this review are a labor of love and admiration for those who have passed on. If they can make the present generation realize the difficulties, the enormous labor and the hardships placed in the path of its dermatologic forbears, which they so gallantly surmounted, I shall be more than repaid.

There may be many "sins of omission" in a relation of this character, but I sincerely believe that there are none of commission, as I have ascertained the accuracy of every fact presented.

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24. Bowen, J. T.: The Epitrichial Layer of the Human Epidermis, Anat. Anz. **4**:412, 1889; Precancerous Dermatoses: A Study of Two Cases of Chronic Atypical Epithelial Proliferation, J. Cutan. Dis. **30**:241, 1912.

PREVALENCE OF SYPHILIS IN THE VIRGIN ISLANDS OF THE UNITED STATES

RESULTS OF A SEROLOGIC SURVEY

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CLEVELAND

Serologic surveys, undoubtedly the most accurate of the various methods of determining the prevalence of syphilis, are limited in precision by certain factors, such as the size and randomness of the sample, the specificity and sensitivity of the tests used and the failure to detect seronegative syphilis.

During the course of epidemiologic studies of leprosy in 1939 and 1940, more than 70 per cent of the inhabitants of the island of St. Thomas and more than 95 per cent of the population of a rural area on the island of St. Croix were examined in clinics. Serologic tests were made on nearly 10,000 persons, representing 60 per cent of the inhabitants of the two areas. This number is felt to be a true random sample, and, furthermore, the serologic tests were considered to be sufficiently accurate and sensitive. Seronegative syphilis remains an unknown quantity. It is the object of this paper to discuss the prevalence of syphilis in the Virgin Islands of the United States as indicated by serologic tests.

DESCRIPTION OF THE AREA

The Virgin Islands of the United States are situated in the Caribbean Sea about 40 miles (64 kilometers) east of Puerto Rico and 1,400 miles (2,253 kilometers) south of New York. There are three main islands in the group, St. Thomas and St. John, which lie together between Puerto Rico and the British Virgin Islands, and St. Croix, which is 40 miles south of St. Thomas. The climate is agreeable and pleasant, the temperature ranging from 68 to 92 F., with an annual mean of 80 F. The average annual rainfall amounts to 46 inches (117 cm.), but frequent and severe droughts occur. The inhabitants number nearly 25,000, of whom only 700 live on St. John while the remainder are about equally

The observations on which this study is based were conducted under the auspices and with the support of the Leonard Wood Memorial and were aided by the Works Projects Administration.

divided between St. Thomas and St. Croix. Approximately 70 per cent of the population are Negroes; more than 20 per cent are of mixed Negro and white strains, and less than 10 per cent are white or Puerto Ricans of mixed blood (West Indian, Negro and white).

The majority of the people on St. Thomas live in the town of Charlotte Amalie, which is essentially urban. St. Croix, on the other hand, is primarily an agricultural community, and most of the inhabitants live in rural surroundings. Economically the islands are poor, and for many years they have been far from self supporting. There is an efficient and active local health department on each island, which provides adequate free medical care for all those unable to pay for it, but only recently has much attention been given to syphilis, so the great majority of persons with syphilis have not been treated. General health conditions in the Virgin Islands compare favorably with other islands of the West Indies. Total and infant mortality rates, although declining steadily during the past twenty-five years, are still high when compared with northern standards. Tropical diseases common in other islands of the West Indies are seldom seen, although filariasis is common on St. Croix. Malaria and dysentery occur infrequently, but yaws is absent. Dietary deficiencies are common, and pellagra and cutaneous and ocular changes due to lack of vitamin A are frequently seen.

METHODS OF STUDY

The procedures were essentially the same on St. Thomas and St. Croix. A house to house census was first made, after which most of the enumerated population were examined in clinics. On St. Thomas the population numbered 10,592, which is some 600 less than the number given by the official census of 1940, owing to the fact that most continental Americans and the members of the United States Marine Corps and their families were not included in the present investigation. Of these, 7,350, or nearly 70 per cent, were examined in clinics. Samples of blood were taken from 6,130, comprising about 83 per cent of the examined group and 58 per cent of the enumerated population. The entire rural population of St. Croix, which numbered about 5,100, was chosen for study; nearly 4,800 persons, or 95 per cent, were examined in clinics. Serologic tests were made on samples from 3,332 persons, representing about 70 per cent of the examined group and 65 per cent of those enumerated. In both areas there was a total population of 15,692; 12,150 were examined in clinics and serologic tests were made on bloods from 9,462, representing 60 per cent of the entire population and 78 per cent of those examined. The untested portion of the

examined group was largest among infants and old persons. But it is felt that the sample tested was truly random as regards age, sex, race, physical condition and economic status and large enough to be statistically significant.

Samples of blood from St. Thomas were sent to the School of Tropical Medicine in San Juan, Puerto Rico, where Wassermann and Kahn tests were performed under the direction of Dr. R. C. Ruiz Nazario. The Wassermann test used was a modification of the Kolmer technic using a cholesterolized alcoholic extract of beef heart as antigen. The Kahn tests were made with a standard Kahn antigen supplied by one of the large manufacturers of biologic products. In most cases in which the results of the tests were positive, partly positive or unsatisfactory, repeated tests were made on fresh samples of blood. In this way some reactions, originally positive or doubtful, were changed to negative. The tests of persons who originally gave completely negative reactions were not repeated; so there was a resulting correction toward the negative side. All samples of blood from St. Croix were subjected only to the Kahn test in one or the other of the two local hospital laboratories under the supervision of Dr. F. Meredith Hoskins. Occasionally duplicate tests were sent to another laboratory on St. Thomas as a check on accuracy and sensitivity. Positive or doubtful results were seldom repeated in the St. Croix group; therefore, no correction toward the negative side occurred as it did in the St. Thomas investigation. The results of Wassermann tests in which there was fixation of complement in one or more tubes sufficient to be called at least 2 plus and the results of Kahn tests showing definite and unmistakable flocculation, even though incomplete, were counted as positive reactions. When both tests were made on the same serum, the result of the Kahn test was chosen to indicate the serologic status.

RESULTS OF TESTS

Satisfactory serologic tests were recorded for 9,462 persons from the two islands. Of these, 1,321, or 14 per cent, had strongly positive reactions and 164, or 1.7 per cent, had partly positive reactions, giving a total of 15.7 per cent with positive reactions. Table 1 shows the results of tests by sex, race and island. On St. Thomas there were 14.5 per cent positive reactions, while on St. Croix there were 18.2 per cent positive reactions. This is a greater difference than would be caused by corrections in the St. Thomas figures due to repeated tests, and greater than would be expected by chance alone (3.7 ± 0.80). On St.

Thomas males showed a slightly higher percentage of positive reactions, but the difference is not statistically significant. On St. Croix the reverse is true, with a higher percentage of positive reactions occurring among the females, but the difference is too small to be of much signifi-

TABLE 1.—*Results of Serologic Tests of Residents of St. Thomas and St. Croix by Sex and Race*

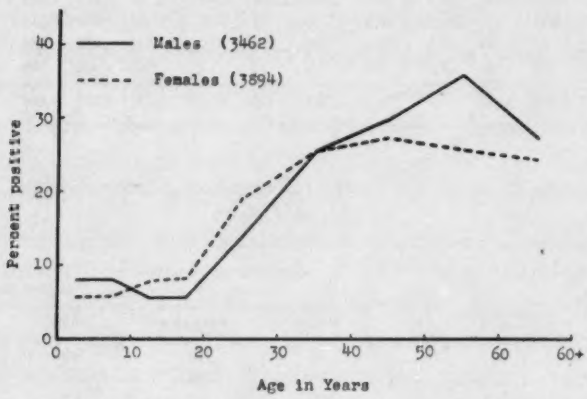
	St. Thomas				St. Croix				Total			
	Number in Group		Percentage of Positive Reactions		Number in Group		Percentage of Positive Reactions		Number in Group		Percentage of Positive Reactions	
Racial Group	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Negro	2,172	2,666	16.4	15.9	1,290	1,228	20.4	22.8	3,462	3,894	17.9	18.1
Mulatto	182	208	15.9	10.6	40	41	15.0	14.6	222	249	15.8	11.3
Puerto Rican	56	93	16.1	8.6	396	296	5.6	9.1	452	389	6.8	9.0
White	409	344	4.6	3.5	27	14	7.4	0.0	436	358	4.6	3.4
Total	2,819	3,311	15.0	14.0	1,753	1,579	16.8	19.9	4,572	4,890	15.4	15.9

TABLE 2.—*Results of Serologic Tests of Negroes of St. Thomas and St. Croix by Age and Sex*

Age Group, Years	Number in Group		Percentage of Positive Reactions	
	Males	Females	Males	Females
0- 4	75	53	8.0	5.7
5- 9	397	394	8.1	6.3
10-14	454	524	5.5	7.8
15-19	406	434	6.1	8.3
20-24	343	340	10.2	19.1
25-29	302	311	17.9	19.0
30-34	194	247	22.2	24.7
35-39	171	243	29.2	26.3
40-44	176	240	31.2	27.9
45-49	195	235	28.2	27.2
50-54	189	239	34.9	25.1
55-59	186	226	37.1	25.5
60-64	166	166	26.5	25.9
65-69	98	106	27.5	22.6
70+	108	136	31.5	23.5
Total	3,462	3,894	17.9	18.1

cance. Among the racial groups, Negroes had much the highest percentage of positive reactions, with the mulattoes next highest, while among Puerto Ricans and white persons the proportion was considerably lower than in any of the others. The results of tests in Negroes from the two areas are given in table 2, which shows the percentage of males and of females with positive reactions (in five year age groups). The

same data are presented graphically in the chart (in five year age groups up to 20 years of age and thereafter in ten year groups). Up to 10 years of age the percentage of boys with positive reactions remained constant and at a higher level than that of the girls, but from 10 to 15 years of age the boys showed a decrease to a level below that of the girls, who showed a slight increase. The proportion of females with positive serologic reactions continued to increase, slowly up to 20 years of age and rapidly thereafter, with a peak of about 27 per cent being reached between 40 and 50 years of age, after which it decreased slightly. The proportion of males with positive reactions began to increase after 15 years of age, slowly up to 20 years of age and rapidly thereafter until a peak of about 37 per cent was reached in the sixth decade, after which there was a slight decrease.



Percentage of Negroes of St. Thomas and St. Croix showing positive serologic reactions.

COMMENT

The incidence of syphilis is about 18 per cent among Negroes of the Virgin Islands of the United States and compares favorably with the incidence in Negroes in the southern United States, where numerous surveys, summarized by Wenger and Ricks,[1] revealed that 20 per cent gave positive serologic reactions, the proportion being slightly higher among females than among males, as it was on St. Croix. Jason[2] reported that 19.4 per cent of Negroes seen at the Freedmen's Hospital in Washington, D. C., had syphilis and stated that among the higher

1. Wenger, O. C., and Ricks, R. C.: The Public Health Aspect of Syphilis in the Negro Race in Certain Southern States, South. M. J. **24**:556-561 (June) 1931.

2. Jason, R. R.: On the Incidence of Syphilis in the American Negro, Am. J. Syph. & Neurol. **19**:313-322 (July) 1935.

social and economic classes the disease was much less common than among the less favored groups. This probably applies to the Virgin Islands as well, where Negroes, with an incidence of syphilis of 18 per cent, represent a lower social group than the mulattoes, with an incidence of syphilis of about 14.5 per cent, while white persons, with a still lower prevalence of the disease, belong, in general, to a more favorable class of society.

The Puerto Ricans represent in part immigrants from the island of Vieques, which is located near the eastern end of Puerto Rico, although some were born on the main island and others were descendants of immigrants born on the Virgin Islands. About 7.4 per cent of Puerto Ricans living on the Virgin Islands gave positive serologic reactions, which is in close agreement with an estimate of a 6 per cent incidence of syphilis for all of Puerto Rico made by Costa Mandry [3] in 1940. On the other hand, Koppisch,[4] on the basis of pathologic and serologic studies, estimated that among the poorer classes of the urban population of Puerto Rico syphilis reached a prevalence of about 21 per cent.

There are some interesting differences in the prevalence of syphilis among Negroes in the two sexes at varying ages. The slightly higher prevalence in males under 10 years of age followed by a slight decrease between 10 and 15 years of age probably indicates that serologic evidence of congenital syphilis is disappearing, because of selective mortality and the reversal of serologic reactions with time, more rapidly than syphilis is being acquired. Among the females, in contrast, the incidence steadily increases, probably because cases of acquired infections exceed the number of cases in which signs of congenital syphilis are disappearing. From puberty to about 35 years of age the prevalence in females rises more rapidly and to a higher level than in males, which suggests greater sexual promiscuity among females. After 35 years of age, the prevalence in males increases more rapidly and to a higher level than in females, reaching its peak between the ages of 50 and 60, which is ten years later than in females. This may result from diminishing sexual activity in females after the menopause, while in males sexual activity is continued for a longer time. The decline in prevalence in old age is doubtless due to the fact that serologic evidence of syphilis is disappearing more rapidly than new infections are being acquired.

In general the same situation was found among Negroes of the Southern states,[1] but there are certain striking differences. There was the same earlier and more rapid increase in prevalence of syphilis

3. Costa Mandry, O.: The Incidence of Syphilis in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. **16**:203-236 (Dec.) 1940.

4. Koppisch, E.: Incidence of Syphilis in Puerto Rico, Puerto Rico Health Bull. **3**:197-206 (May) 1939.

in females, but a peak of 34 per cent was reached at 20 to 24 years of age, while in males the peak of 32 per cent was reached at 25 to 29 years of age, a gradual decrease occurring after the peak in both sexes, until the incidence in old age was about half that found in young adult life. The greatest prevalence in Southern negroes was reached at an age about 20 years under that in Negroes of the Virgin Islands. Maxcy [5] explained the early peak in Southern Negroes on the basis of greater sexual promiscuity between the ages of 15 and 25 years, with a decline in infection later due to monogamous family relationships. He stated the belief that the disappearance of serologic evidence of disease with time accounts for the major part of the decline and that only a small part could be attributed to specific therapy or selective mortality. Among Negroes of the Virgin Islands continued monogamous family relationships are the exception rather than the rule, which probably accounts for the continued rise in the incidence of syphilis to a peak later in life. The decline in prevalence in old age is not nearly as striking in the Virgin Islands as in the South, probably because the Negroes on the Virgin Islands acquire more new infections later in life. What decline there is can be attributed almost entirely to the spontaneous disappearance of serologic signs of syphilis or to selective mortality, because only a small fraction of persons with syphilis have received any specific therapy.

Congenital syphilis doubtless is the cause of practically all of the positive serologic reactions of children under 10 years of age and in most of those of children under 15 years of age, although it is probable that syphilis is occasionally acquired before these limits, especially in females. However, the disappearance of serologic evidence of congenital syphilis tends to balance the incidence of newly acquired infections, so that the percentage of children under 15 years of age with positive serologic reactions is a fair estimate of the incidence of congenital syphilis when yaws is not a factor. Among Negroes of the Virgin Islands less than 15 years old 7.1 per cent of females and 6.8 per cent of males gave positive reactions, while for Negroes of the Southern states [1] the figures were essentially the same, 9 per cent for females and 8.1 per cent for males.

In Kingston, Jamaica, in 1937 Whitbourne and Saunders [6] observed that among 1,100 school children 4.2 per cent of the girls and 3.6 per cent of the boys gave positive serologic reactions, but they estimated that yaws caused part of the positive reactions and that only about 2.4 per cent of the boys and 3 per cent of the girls had congenital syphilis.

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5. Maxcy, K. F.: A Serological Survey for Syphilis in a Negro Population, South. M. J. **27**:891-901 (Nov.) 1934.

6. Whitbourne, D., and Saunders, G. M.: Incidence of Syphilis Among School Children of Kingston, Jamaica, Brit. M. J. **1**:1108-1110 (May 29) 1937.

This would indicate that among the Negroes of the Virgin Islands there is more syphilis than among the Negroes in Kingston, Jamaica, and it is interesting to speculate on the reasons for the difference. Both localities represent shipping centers in the West Indies, and the population groups are essentially the same, yet judging from the data available syphilis appears to be about twice as prevalent in the Virgin Islands as in Jamaica. In Jamaica it is possible that the high prevalence of yaws tends to protect the population against infection with syphilis, while in the Virgin Islands, where yaws does not occur, this protective influence is lacking.

SUMMARY

During the years 1939 and 1940 a serologic survey was made in the Virgin Islands of the United States.

Samples of blood were taken from 9,462 persons, representing 60 per cent of the entire population studied and 78 per cent of persons examined in clinics.

Of the persons tested, 1,485, or 15.7 per cent, had positive serologic reactions.

Eighteen per cent of the Negroes, 14.6 per cent of the mulattoes, 7.4 per cent of the Puerto Ricans and 4 per cent of the white persons had positive reactions.

Among residents of St. Croix, 18.2 per cent had positive reactions, while among the St. Thomas group, 14.5 per cent had positive reactions.

Among Negroes the proportion with positive reactions increased earlier in life in females than in males and reached a peak of about 27 per cent in the age group between 40 and 50 years. For males the peak of about 36 per cent was reached a decade later. Both sexes had a slight decrease in positive reactions in older age groups.

Dr. Knud Knud-Hansen, Commissioner of Health for the Virgin Islands of the United States, allowed these studies to be made in the Virgin Islands, gave advice and permitted the former Municipal Physicians of St. Thomas, Dr. F. Meredith Hoskins and Dr. John Moorhead, to assist in the clinic examinations. Dr. Walter Corey, of the United States Public Health Service, also examined many of the patients on St. Thomas. On St. Croix, Dr. Norman Sloan, formerly Assistant Municipal Physician, spent much time in the clinics, and Dr. Ricardo Guinto, Associate Epidemiologist of the Leonard Wood Memorial, spent his entire time examining patients during four months of 1940. Dr. George Bachman, Director of the School of Tropical Medicine in Puerto Rico, provided laboratory facilities for the serologic tests of the group on St. Thomas. The tests were performed under the direction of Dr. R. C. Ruiz Nazario. Dr. F. Meredith Hoskins, Chief Municipal Physician of St. Croix, supervised the Kahn tests on St. Croix.

SOLUTION OF ALUMINUM CITRATE AS A SUBSTITUTE FOR SOLUTION OF ALUMINUM ACETATE N. F.

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Solution of aluminum acetate N. F. (Burow's solution) is a clear, colorless, weakly acid liquid with a faintly acetous odor and a sweetish, astringent taste. It contains in each 100 cc. not less than 4.8 Gm. and not more than 5.8 Gm. of aluminum acetate. According to the sixth edition of the National Formulary, the solution is prepared as follows:

Lead acetate	150 Gm.
Aluminum sulfate	87 Gm.
Water, a sufficient quantity to make	1,000 cc.

Dissolve each salt separately in 525 cc. of water, and mix the cold solutions by pouring the lead acetate solution in a thin stream, with constant stirring, into the aluminum sulfate solution. Set the mixture aside in a cold place (about 10° C.) for 24 hours. Siphon off 1,000 cc. of the clear liquid, or, if necessary, transfer the magma to a filter and add sufficient water through the magma to make the product measure 1,000 cc.

Note: This solution should be dispensed only when clear.

The usefulness of solution of aluminum acetate N. F. in the treatment of certain cutaneous diseases is well known to most dermatologists. In an excellent review of the role of this solution in dermatology, Combes [1] ascribed its virtues to its buffer action, its astringent and antiphlogistic properties and its antiseptic action. It is capable of maintaining its hydrogen ion concentration in spite of the addition of appreciable quantities of acids or alkalis. The solution used in compresses not only neutralizes the alkaline secretions of exudative dermatoses but also, as the skin is capable of absorbing acids, replaces the acids in the epidermis, thereby maintaining the natural defensive mechanism of the integument against pyogenic infection. The astringent properties of solution of aluminum acetate are well known. A mild effect of this type is of value in cutaneous inflammations accompanied by edema and exuda-

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1. Combes, F. C.: The Role of Burow's Solution in Dermatology, New York State J. Med. **40**:37-42 (Jan. 1) 1940.

tion, both by contracting the blood capillaries and coagulating the albumin in the tissue fluids, thus controlling exudation. Combes failed to offer any evidence of the antiseptic power of the solution but stated that it tends to maintain an actual acidity unfavorable to bacterial proliferations.

That solution of aluminum acetate N. F. even when properly diluted may be irritating to some patients cannot be denied. Combes expressed the possibility that free lead acetate, not precipated because of an insufficiency of aluminum sulfate, may be the responsible factor. He stated that 87.84 Gm. of aluminum sulfate is required to precipitate 150 Gm. of lead acetate instead of 87 Gm., as specified in National Formulary VI. In discussing Combes's paper, Sulzberger stated that in the cases of irritation observed by him the lead was not the cause. His patients were sensitive to aluminum salts, reacting to such substances as aluminum chloride as well. Both physicians stressed the great variation in composition and in therapeutic action of solution of aluminum acetate N. F. obtained at different drug stores.

The time and labor elements in preparing the official solution are also disadvantages. More than twenty-four hours is required for its preparation according to the specifications of the National Formulary. When one considers the frequent use of solutions of aluminum acetate in acute inflammations of the skin, this is a decided disadvantage. As a result, the small drug store with an inactive prescription department is apt to keep a stock bottle of the solution on hand for months. Usually after it has stood for a time a flocculent, jelly-like precipitate of aluminum hydrate develops in the solution, and if the solution is dispensed without being clarified the precipitate has an unfavorable psychologic effect on the patient. The solution may be cleared by the addition of a little boric acid or sodium borate, which of course changes the composition of the preparation.

A substance of constant composition which exhibits the favorable properties of the solution of aluminum acetate and which can be easily prepared is a worth while addition to the dermatologic armamentarium. For more than a year we have been using solution of aluminum citrate in clinic and in private practice as a substitute for solution of aluminum acetate N. F. It possesses the advantages of the official solution without its unfavorable features. While it has not been tolerated in every case, we have the distinct impression that complaints have been much less frequent and that its action has been more constant. Furthermore, some of the failures, we feel, have been due to prescribing the preparation in a form unsuitable for the condition in question, for example, prescribing a lotion when compresses were more properly indicated.

Aluminum citrate contains 12.48 per cent aluminum and is commercially available as a glassy crystalline substance which may be readily

ground to a fine white powder. As a rule it contains about 10 per cent water. It is slowly soluble in cold water, but in hot water there seems to be almost no limit to its solubility. Solutions containing 1 kilogram per liter have been made with no crystallization on cooling. If the concentration is sufficiently high the solution may be slightly opalescent. Heat must be applied carefully to effect solution, for too high a temperature may char the undissolved compound. Likewise, this substance is easily soluble in ammonia water.

METHODS OF APPLICATION

It must be stated here that our experience with aluminum citrate has been strictly clinical. No attempt has been made to study the physiologic properties of the salt or its effects on animals when applied locally. As it had been used commercially in deodorant creams and foot powders, we felt reasonably certain that it would not harm the human skin in the strength to be applied by us.

Since aluminum acetate, with a molecular weight of 204.0, contains 13.22 per cent aluminum and aluminum citrate, with a molecular weight of 216.0, contains 12.48 per cent aluminum, slightly more of the latter will have to be used to secure the same astringent effect as with the former. Then, too, aluminum citrate as purchased contains approximately 10 per cent water. Taking these differences into consideration, we estimated that a 6 per cent solution of aluminum citrate contained approximately the same quantity of aluminum as solution of aluminum acetate N. F., which is a 4.8 to 5.8 per cent solution.

Having chosen a 6 per cent solution of aluminum citrate as the approximate equivalent of solution of aluminum acetate N. F., we felt that perhaps some economies could be effected by dispensing the citrate solution in a more concentrated form when intended for use as wet compresses. We decided on a 36 per cent solution, which is approximately six times as strong in aluminum content as the official solution. This means that clinically 1 teaspoonful (5 cc.) of a 36 per cent solution of aluminum citrate has the same astringent and allied properties as 2 tablespoonfuls (30 cc.) of solution of aluminum acetate N. F. We have made a practice of prescribing ½ to 2 ounces (15 to 60 cc.) of the 36 per cent solution of aluminum citrate. Of this, 1 teaspoonful is ordered to be diluted with 10 to 16 ounces (300 to 475 cc.) of water, just as formerly we had ordered 2 tablespoonfuls of the aluminum acetate solution to be so diluted. The application of compresses wet with this substance is carried out in a fashion similar to that used with solution of aluminum acetate N. F.

Aluminum citrate may be successfully incorporated into lotions when it is desired. While consideration of its properties will suggest many

formulas, one with good keeping qualities that we have found useful is as follows:

Boric acid	4.0 Gm.
Zinc oxide	30.0 Gm.
Solution of aluminum citrate, 6 per cent	20.0 cc.
Hamamelis water N. F.	60.0 cc.
Water, a sufficient quantity to make	240.0 cc.

To this stock lotion may be added more zinc oxide, talc, resorcinol, phenol and glycerin without disturbing its stability. Solution of coal tar N. F. may be included just before the lotion is to be used, because it gradually precipitates the aluminum salt. In preparing lotions containing aluminum citrate we do not recommend the use of solution of calcium hydroxide U. S. P., for that also brings about a slow gelatinous precipitation of aluminum hydrate.

An aluminum citrate paste may be formulated as follows:

Solution of aluminum citrate, 6 per cent	10.0 cc.
Wool fat	20.0 Gm.
Paste of zinc oxide N. F.	30.0 Gm.

This is a modification of the well known Burow's paste, made with aluminum acetate, and has the same indications as the latter. It may be modified by the addition of antipruritic substances, such as phenol, menthol and solution of coal tar N. F., as well as other medicaments.

Fine ointments containing aluminum citrate may be made by mixing the 6 per cent solution in a hydrous wool fat and petrolatum base or, better, with an aqueous absorbent. We have used the following cream with satisfactory results:

Solution of aluminum citrate, 6 per cent	7.5 cc.
Oxycholesterol-petrolatum base, a sufficient quantity to make	30.0 Gm.

The amount of the solution may be increased to 50 per cent if desired and, as with the paste previously described, phenol, menthol, solution of coal tar N. F., and other agents may be added in appropriate concentrations.

SUMMARY

We have successfully substituted solution of aluminum citrate for solution of aluminum acetate N. F. in clinic and private practice. Two stock solutions of aluminum citrate are maintained. For economic reasons, a 36 per cent solution is dispensed for use in wet compresses. One teaspoonful (5 cc.) of this solution is equivalent to 2 tablespoonfuls (30 cc.) of solution of aluminum acetate N. F.; therefore, 1 teaspoonful must be diluted with 10 to 16 ounces (300 to 475 cc.) of water before using.

A 6 per cent solution is used as a substitute for the official solution of aluminum acetate for all other purposes. These include the making of lotions, pastes and creams. Excellent stable preparations may be made with therapeutic efficacy equivalent to that of similar substances made with solution of aluminum acetate N. F.

The use of solution of aluminum citrate insures more uniform composition and clinical effect than those of solution of aluminum acetate N. F. This salt may be purchased as a glassy crystalline substance, and fresh solutions can be made readily at a great saving of time and labor as compared with making the official preparation.

411 Walnut Street.

THRESHOLD ERYTHEMA DOSE OF ROENTGEN RAYS

I. REVIEW OF THE LITERATURE AND COMMENT ON VARIATION OF DOSES IN USE IN AUSTRALIA, THE UNITED STATES AND ENGLAND

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During the past few years the differences in values of the erythema dose reported in the medical literature have varied so much that one of us (Belisario) began in 1937 to investigate the reasons for these discrepancies. This work led finally to an experimental program which resulted in the formulation of a standard threshold erythema dose which can be recognized by workers throughout the world with greater accuracy than any value employed in the past.

Although begun in Australia, the investigation finally included personal visits to many dermatologic centers in Great Britain and in the United States and correspondence with members of many more. In order to correlate properly the erythema values in use in the three countries, it was considered necessary to talk to the dermatologists personally, see their machines and tubes in action and observe at first hand the type and degree of reactions that were called erythema doses. Seventy-five dermatologists and some radiologists were visited in the United States and thirty dermatologists and radiologists in Great Britain.

The previous literature has contained little material correlating experimental results and physical data with the application in routine dermatologic practice; as a result there was no choice but to accept the more or less arbitrary standard of some authority, often without a clear conception of the criterion of reaction used. Our work attempts to establish a rational basis for the criterion chosen and to correlate physical data with clinical observations in order that the concept of erythema dose may be clarified and then considered according to its clinical merits.

The two parts of this paper cover the various phases of the whole investigation. In the first part are a discussion of the investigations of various authorities from 1896 to the present, dealing with the subject

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of the roentgen ray erythema dose (whether threshold or otherwise), showing the advantage of using the threshold value if properly standardized and indicating the errors which other standards seem to foster, and a discussion of the personal observations made during visits to dermatologic centers in Australia, the United States and Great Britain and of the correspondence with colleagues in these countries, showing the wide variations in the standard in present use and the possible causes of the discrepancies and pointing out the importance of a rational standard. The second part contains an account of the results of the experimental program carried out by one of us (Belisario), which has extended over two years, the presentation of a new standard threshold erythema reaction, an account of the investigation of various details of sensitivity and a discussion of idiosyncrasy and observations on the "pseudo-erythema reaction."

REVIEW OF THE LITERATURE

1896 to 1929.—In this period, before the establishment of a standard unit of radiation in terms of ionization, the erythema dose provided the only means of standardization of dosage. Even at present many dermatologists use the erythema dose as a means of measurement, and most of the dermatologic literature until the past few years has been written almost exclusively in these terms. Radiologists and therapeutists using higher voltage roentgen radiation have been more inclined to use the roentgen unit since its adoption, in 1928, because cutaneous reactions are not as fundamentally important and significant in this form of therapy as they are in cutaneous therapy. Recently, however, even in this field the actual "tissue dosage" or "tumor dosage" has been determined in terms of erythema dose since that is the only physiologic criterion of the effect of radiation that is available. Since the radiation absorbed by tissues at a considerable depth is calculated as the percentage of the radiation absorbed by the skin, even "depth doses" or "tissue doses" may logically be expressed in terms of erythema dose.

Visible cutaneous effects depend on three factors: (*a*) the radiation in the direct beam from the x-ray tube, (*b*) the radiation scattered back from underlying tissues (back scatter) and (*c*) the "volume effect," or the relative volume of tissue injured. The last-mentioned factor has received scant recognition in the literature, but in part 2 of this work it will be discussed in more detail and its importance emphasized.

The erythema dose as a criterion of reaction to radiation has developed more or less independently in dermatology and in high voltage roentgen ray therapy with little mutual interest, and the chronologic developments in both fields are included in the following discussion.

One of the first to suspect that dermatitis following irradiation was due to the roentgen rays was Bowles,[1] in 1896, and the first case of this kind was reported by Stevens.[2] Gilchrist[3] and Kibbe[4] in 1897 made microscopic studies of the histologic changes, and their work was probably as complete and accurate as any since that time. The early workers were familiar with the sequence of events, i. e., pigmentation, telangiectasis, atrophy, chronic dermatitis, keratoses and ulceration. Kienböck[5] in 1900 enclosed rats in metal cylinders, excluding light and electrical effects, and still produced reactions, which demonstrated that the roentgen rays themselves produced the biologic effects observed.

Kronig and Friedrich in 1918 found the erythema reactions from equal doses given in widely different times of exposure (intensities) to be very different; the reaction to the shorter exposure of higher intensity was more severe. The significance was not realized for many years but was emphasized later by Regaud, Holthusen, Liechti and others between 1922 and 1933. Apparently the effect was noticeable if the extremes of intensity were in the ratio of 1 to 8 but not if they were in the ratio of 1 to 5. This question was investigated, and in part 2 of this paper it will be shown that the results of experiment seem to indicate that in the range of intensities used in practice (27 to 150 per minute) the reactions are independent of intensity.

As early as 1922 Erskine[6] pointed out that there is only a slight visible difference when the threshold erythema dose is doubled. As a result of this observation, made independently, of course, by many investigators, innumerable criteria of visible reactions were reported in the literature. Holfelder[7] in 1922 gave the unit of biologic effect in Germany as the maximum dose which would just fail to produce permanent ill effects on the abdomen of a middle-aged patient as his "standard skin dose" (*Haut-Einheits-Dosis* of Seitz and Wintz, or unit skin dose). The danger of serious sequelae from irradiating subjects with such a standard for test purposes is obvious. Furthermore, minor variations

1. Bowles, R. L.: The Sunburn of X-Rays, Lancet **1**:665, 1896.

2. Stevens, L. G.: Injurious Effects on the Skin, Brit. M. J. **1**:998, 1896.

3. Gilchrist, T. C.: A Case of Dermatitis Due to the X-Rays, Bull. Johns Hopkins Hosp. **7**:71, 1897.

4. Kibbe, A. B.: A Case of Dermatitis Caused by Roentgen Rays, with Results of Microscopic Examination of the Affected Skin, New York M. J. **65**: 71, 1897.

5. Kienböck, R.: The Effect of Roentgen Light upon the Skin, München. med. Wchnschr. **45**:1581, 1900.

6. Erskine, A. W.: Minimum Erythema Dose with Diagnostic Voltages, Am. J. Roentgenol. **9**:479, 1922.

7. Holfelder, H.: Underlying Principles in Radiotherapy of Malignant Tumors, Am. J. Roentgenol. **9**:342, 1922.

in such a violent reaction could not be detected. Failla, Quimby and Dean [8] in the same year defined a standard reaction at the other, safer and more logical, extreme, namely, a threshold reaction. They employed the erythema reaction as a biologic indicator for radium irradiation with various filters. They found that the degree of erythema produced on different patients by the same dose was not always the same, so they standardized a dose which produced no visible effect on the less radiosensitive persons and a slight but definite effect on the more radiosensitive ones. MacComb and Quimby [9] much later defined this standard pigmentation dose as that quantity of radiation which when delivered in one exposure at the rate of from 40 to 60 r per minute produced in 80 per cent of all patients a visible pigmentation within two to four weeks and in the other 20 per cent no visible reaction. Thus a definite end point is established without the necessity of the observer specifying a degree of reaction.

Martius about the same time reported a difference of 66 to 258 per cent in the unit skin dose of various investigators; at even this early date the discrepancies were enormous. The fact that a wide range of values are still in use prompted the present investigation.

Weatherwax and Leddy [10] in 1923 pointed out that only ionization measurements on the surface of the skin would indicate the dose producing the erythema, since both the direct beam and back scatter contribute radiation energy to the area of skin being exposed. It was not till fifteen years later that the extrapolation chamber developed at Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, made it possible to determine accurately the amount of back scatter for various areas without the errors incident to measurements with a large thimble chamber on a surface. About this same time several separate groups of investigators began serious study of the mechanism and definite measurement of this biologic reaction.

Miescher,[11] in 1923 and 1924, described the erythema as occurring in waves. He stated the belief that three, or possibly four, waves occurred, any or all of which might be sufficiently great to be clinically recognizable. He described the first wave as corresponding with the early reaction; it

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8. Failla, G.; Quimby, E. H., and Dean, A. L.: Some Problems in Radiation Therapy, Am. J. Roentgenol. **9**:479, 1922.

9. MacComb, W. S., and Quimby, E. H.: The Rate of Recovery of Human Skin from the Effects of Hard or Soft Roentgen Rays or Gamma Rays, Radiology **27**:196-207, 1936.

10. Weatherwax, J. L., and Leddy, E. T.: Standardization of Ionization Measurement of Intensity and Measurement of Scatter Effective in Producing Erythema, Am. J. Roentgenol. **10**:488, 1923.

11. Miescher, G.: Erythema Due to Roentgen Rays, Strahlentherapie **16**:333, 1923.

appeared on the first or second day and usually disappeared by the fourth day. The second wave occurred from the eighth to the twenty-second day, and the third wave from the thirty-fourth to the one hundred and fifty-seventh day (the latter period might also include a fourth wave). He found that with small doses one or more of these waves failed to appear but that the wave obtained most frequently was the first one. In part 2 of this paper the results of the experimental work of Belisario will be shown to confirm certain of these observations.

Pohle,[12] in 1926, studied the cutaneous blood vessels after the application of one erythema dose of unfiltered roentgen rays, employing Mueller's skin microscope. He found that moderate doses of roentgen rays of longer wavelength tended to produce an immediate dilatation of the capillaries, while those of shorter wavelength either did not affect the blood vessels at all or caused a slight constriction with gradual dilatation, the maximum effect occurring in six days. With the longer wavelengths the dilatation occurred within six hours, increased for two days and then temporarily receded. The dilated capillary loops visible with the erythema reaction on the sixth day began to recede on the ninth day. Pigmentation in the third week and normal capillaries in the sixth week were observed. After three months the skin appeared entirely normal. With shorter wavelengths and doses considerably greater than the threshold erythema value, the capillaries were still dilated after three weeks, and pigmentation was present. Deep tanning was observed in six weeks, and complete restitution of the cutaneous blood vessels never took place. This study of the actual appearance of the capillaries apparently fits in well with the gross appearance observed by most workers.

Meyer and Glasser [13] in 1926 pointed out the discrepancies in the ionization units used in determining the doses in the various erythema investigations. This was remedied in 1928 by the adoption of the international roentgen unit (r). They observed that the dose required to produce a given biologic effect depended on the quality or wavelength of the radiation and to a certain extent on the relative intensity. Packard,[14] however, in 1927 concluded that equal doses delivered with equal intensity but of different wavelength produce the same quantitative biologic effect on Drosophila eggs; the fact that this observation differs from that of erythema observations is undoubtedly due to the fact that the physical and physiologic conditions involved were different.

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12. Pohle, E. A.: Studies of the Roentgen Erythema of the Human Skin, Radiology **6**:236, 1926; **8**:185, 1927.

13. Meyer, W. H., and Glasser, O. A.: Erythema Doses in Absolute Units, Radiology **6**:320, 1926.

14. Packard, C.: The Quantitative Biological Effects of X-Rays of Different Wave Lengths, J. Cancer Research **11**:1, 1927.

Failla [15] in 1929 aptly summed up the relation between physical, biologic and clinical results by stating that the purely physical aspects, while important, did not play a preponderant part. This was evident from the fact that *purely physical* experiments could reveal nothing about the biologic effects of radiation. On the other hand, biologic effects and clinical results could not possibly be interpreted properly without a certain knowledge of the physics of radiation treatment. Certainly biologic reactions cannot be compared throughout the world unless there is some other unit by which the dose can be measured and known to be the same. Biologic reaction standards reported in the literature have varied from faintly visible reactions (pigmentation or reddening), at the one extreme, to reactions just short of permanent cutaneous damage, at the other extreme. Warnekros even proposed as a standard a reaction which involved a pronounced dark red coloring of the irradiated abdominal wall with separation of the epidermis and a profuse secretion from the raw surface.

1930 to 1940.—From 1930 to the present the trend has been to attempt to correlate the erythema dose with the corresponding dose in international roentgens, but this has been complicated by the many different standards of erythema reaction used by the different investigators.

Erskine [16] estimated the minimum erythema dose for untanned skin, using fields 1 cm. in diameter, as 250 r with unfiltered radiation at 130 kilovolts. Ullmann [17] reported epilation of the scalp with 320 r (including back scatter) and defined his erythema dose as one and one-fourth times the epilation dose, or 400 r (including back scatter). He neglected back scatter for areas of 1 sq. inch or less. These are among the first reports in terms of the international roentgen, but the determination of back scatter with a thimble chamber on the surface was shown later by the Memorial Hospital workers to be subject to many errors, so the values of Ullmann may actually have been slightly different. The same qualification applies to the values of Erskine [18] published in 1931; he stated that an increase in the size of the field increased the reaction at the center of the field until an area of 15 sq. cm. was reached, owing to secondary radiations from the body, which were greater with filtered radiation at long target-skin distances than with unfiltered radiation at shorter distances. This is in accord with the later work at Memorial

15. Failla, G.: The Measurement of X-Ray Dosage by Physical Means, Radiology **13**:293, 1929.

16. Erskine, A. W.: Fewer Variable Factors in Roentgen Therapy, Radiology **14**:317, 1930.

17. Ullmann, H. J.: Fundamentals of Roentgen Ray Treatment, Radiology **14**:28, 1930.

18. Erskine, A. W.: Quality Versus Erythema, in Practical X-Ray Treatment, St. Paul, Bruce Publishing Company, 1931.

Hospital, which showed that the amount of back scatter was less for the quality of radiation used for therapy of the skin than for 200 kilovolts with a 0.5 mm. copper filter. Erskine noted that greater doses of short wavelength radiation were necessary than of long wavelength radiation to produce equal reactions and, further, that the skin would recover from larger doses of long wavelength radiation than of short wavelength radiation, because the latter did more damage to subcutaneous tissues. He stated the belief that the most rational unit of dosage was the erythema dose and pointed out that 10 X (Kienböck), 5½ H (Holzknecht) and tint B (Sabouraud) all gave varying degrees of redness of the skin, whereas "if radiotherapists could agree as to the biologic effect of a standard erythema dose it would simplify matters and tend to reduce an apparent discrepancy." The technic recommended by Erskine for experimentally determining the erythema dose was as follows: A sheet of lead with five circular openings, each 1 cm. in diameter, was laid over the flexor surface of the forearm. All five areas were exposed to a dose of roentgen rays which would *not* produce a reaction; one area was then covered and 20 per cent more radiation was given to all the others. This was repeated until each of the areas had received progressively more radiation in steps of 20 per cent. He found blonds more susceptible than brunets, although the difference (about 15 per cent) was not great. Parts ordinarily covered with clothing were found to be more sensitive than the hands or face. Places where two cutaneous surfaces came into contact were generally more sensitive, and a true idiosyncrasy, though rare, was encountered in a few persons. He observed a latent period of three to ten days after treatment before visible effects were seen.

Nisbet and Keatinge [19] defined reactions ranging from a slight blush within seven to ten days, followed by no sequelae, through various stages of redness, some of which appeared in twenty-four to forty-eight hours, some in three to seven days, followed by vesication and subsequent desquamation and pigmentation. They listed the following factors which had to be considered: 1. The reaction is more intense in younger patients. 2. Blonds should be treated with more care than brunets. 3. There is danger in irradiating sites where sebaceous glands abound. 4. General diseases, such as diabetes and exophthalmic goiter, may influence reactions. 5. Idiosyncrasy definitely does occur. They stated that the erythema dose could be a most useful biologic guide in high voltage roentgen ray therapy if it were properly defined and mentioned the various factors which would influence its interpretation, such as voltage, filter, area of skin, target-skin distance, thickness of tissue and use of single or divided doses.

19. Nisbet, A. T., and Keatinge, L.: Some Observations on the Problem of the Erythema Dose, J. Cancer Research Com., Univ. Sydney **3**:8, 1931.

Reisner [20] in 1932 studied the reactions following the fractional administration of large doses of roentgen rays and claimed that the daily observation of the erythema reaction on human skin was of much greater value than parallel research on plants and animals.

Hess [21] in 1932 advocated ionization dosimetry for superficial therapy and stated that a half value layer of between 0.25 and 1.0 mm. of aluminum was best suited for therapy of the skin. He regarded 400 r with a half value layer of 1.0 mm. of aluminum as the epilation dose and 700 to 800 r as the erythema dose. This is obviously a maximum tolerance dose and agrees almost exactly with that estimated by Molesworth.[22]

Two more important contributions appeared at this time on the mechanism and precise measurement of erythema reactions. Pohle and Wright [23] published the third of their series of experiments on capillary reactions, this one dealing with combined roentgen ray and ultraviolet reactions. They showed that the ultraviolet reaction disappeared permanently in a short time, while the roentgen ray reaction appeared in several cycles over weeks and months, the capillaries showing typical changes. They concluded that ultraviolet radiation enhanced the effect of roentgen rays on the skin, at least temporarily. In part 2 of the present paper the results of experiments with roentgen rays combined with ultraviolet rays and also roentgen rays combined with infra-red rays will be reported.

Harris, Leddy and Sheard [24] in 1932 investigated the cutaneous reaction by means of a spectrophotometer with which the color of the skin could be exactly analyzed. The color of normal skin was expressed in terms of its attributes: (*a*) brilliance (relative luminosity), (*b*) hue (dominant wavelength) and (*c*) saturation (purity). Hue and saturation were considered interdependent, hue being qualitative, saturation quantitative. For normal subjects Sheard and others observed that hue, saturation and percentage of red, green and violet remained fairly constant but that brilliance decreased with increasing amounts of pigment. The dominant wavelength was 5,850 angstrom units, saturation 40 to 50

20. Reisner, A.: The Skin Erythema: Course in Fractional Administration of Large Amounts of Radiation, Fortschr. a. d. Geb. d. Röntgenstrahlen **45**:293, 1932.

21. Hess, P.: Ionization Dosimetry in Superficial Therapy, Röntgenpraxis (no. 17) **4**:748, 1932.

22. Molesworth, E. H.: Personal communication to Dr. Belisario.

23. Pohle, E. A., and Wright, C. E.: Studies of Roentgen Erythema of Human Skin: Microscopic and Skin Capillary Changes After Combined Exposure to Roentgen Rays and Ultra-Violet Rays, Radiology **14**:351, 1930.

24. Harris, M.; Leddy, E. T., and Sheard, C.: Spectrophotometric Analysis of Color of Skin Following Irradiation by Roentgen Rays, Radiology **19**:233, 1932.

per cent and brilliance 45 per cent for blonds and 17 per cent for Negroes. The variation in color of different parts of the body and in different persons (except in exposed areas where there was congestion of the superficial vessels) depended only on variation in brilliance. They also found that blood in the capillaries exerted a considerable influence on the color of the skin. When the skin was abnormal with an abundance of oxygenated blood near the surface there was a shift of the hue toward the red. When there was cyanosis, in which reduced hemoglobin predominated, the hue shifted toward the blue. By this method they could detect the difference in color when the hand was held above or below the heart level.

They mentioned that Holzknecht in 1903 had described the premature reaction which occurred a few hours to a few days after exposure and which was followed by the true reaction on about the eleventh day. They also pointed out that Kohler had first described the premature reaction and had stated the belief that it was due to heat waves from the tube but that Brauer in 1911 had concluded that it was part of the real roentgen ray effect and that the pigment changes which followed were due to the effect on the pigment-forming mechanism itself.

Harris, Leddy and Sheard pointed out that Miescher in 1924 had described the erythema as occurring in waves which appeared (*a*) the first or second day, (*b*) the eighth to the twenty-second day, (*c*) the thirty-fourth to the fifty-first day and (*d*) after fifty-eight days, respectively, after the administration of five or six different doses of each of four qualities to an area 4 by 4 cm. in size on the thigh. The third wave was most intense. The latent period between waves was more apparent than real and tended to disappear with heavier doses. Variations of 700 per cent in different persons were noted between the threshold reaction and erosion. The color of the skin or hair of the subject apparently had no effect. These observations were confirmed also by Pohle with the skin capillary microscope. Harris, Leddy and Sheard used 8 by 8 cm. fields on the lateral aspect of the left leg, with 135 kilovolts, 5 milliamperes, 40 cm. target-skin distance, 25 r per minute, for a total of 520 r (measured in air), and a half value layer of 6.1 mm. of aluminum. This gave their threshold erythema dose, i. e., slight redness in 80 per cent of the subjects. Spectrophotometric readings were taken immediately before irradiation and daily (as long as possible) thereafter. The red excitation value—or the quantitative attribute, saturation—was used to determine the degree of erythema, and brilliance, or relative luminosity, was used to determine the pigmentation. The course of color excitation was cyclic, the first wave showing a maximum in an average of two and five-tenths days, with the succeeding lowest depression occurring at six days,

corresponding with Miescher's observations. The second wave showed a maximum in an average of fifteen and six-tenths days, with the following minimum at an average of twenty-two days, corresponding to Miescher's second wave. The third wave showed a maximum in an average of thirty-two days, with the minimum at an average of forty-five and five-tenths days, and was less pronounced than the second, whereas Miescher's third wave was from the thirty-fourth to the fifty-first day and was the most intense of the waves. Miescher could not visually have separated erythema from pigmentation, and this might have accounted for the discrepancy; by means of the spectrophotometer they could be separated, and each was found to be cyclic but independent of each other. The dominant wavelength, or hue, remained practically constant, and purity, or saturation, paralleled erythema, owing to an increase in the quantity of blood in the peripheral vessels. Erythema must be due to a more complete opening of the capillaries and to a greater number of open capillaries in the skin allowing more normal blood to be present. Since erythema and the effect on the capillaries was rhythmic, it cannot be assumed to be directly due to a single dose of roentgen rays acting for a short time, because in such a case the effect would be expected to deteriorate at a fairly constant rate rather than to show the intermittent maxima, as observed. The observations tend to indicate that the erythema reaction must be due to some complicated secondary effect of the radiation.

Knox and Levitt [25] in 1932 mentioned that an early erythema occurred in a considerable proportion of cases and might appear as early as half an hour after irradiation or at any time up to forty-eight hours. They also noted that the erythema dose was about half the dose which just failed to produce blistering, or, in other words, that slightly more than twice an erythema dose would produce blistering. Their erythema standard evidently was considerably greater than a threshold erythema.

Eller and Mutscheller [26] gave 340 r as the average threshold erythema dose of about seven therapeutists around New York.

In a symposium from Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, in 1933, Failla [27] stated that the general belief among radiologists was that accuracy in determining the erythema dose was practically impossible but that after making thousands

25. Knox, R., and Levitt, W. M.: A Text Book of X-Ray Therapeutics, London, A. & C. Black, Ltd., 1932, p. 64.

26. Eller, J. J., and Mutscheller, A.: Dosage of Skin Therapy Expressed in International Roentgen Units, Arch. Dermat. & Syph. **27**: 670 (April) 1933.

27. Failla, G.: Relative Effects Produced by 200 KV. Roentgen Rays, 700 KV. Roentgen Rays and Gamma Rays: VII. Correlation of Experimental Results, Am. J. Roentgenol. **29**:352, 1933.

of tests they had developed a system at Memorial Hospital which was accurate within 10 per cent. Duffy, McNattin, Copeland and Quimby [28] in the same symposium remarked that a biologic unit of radiation could not be based on cutaneous tolerance, because it is impossible to establish an end point; there are all gradations of first and second degree reactions. Since the skin of different subjects shows varying reactions to the same dose, the personal element can be eliminated by observing the dose which will just produce a visible reaction and then adjusting the dose so that the range of response of different persons produces a visible change in 80 per cent and no change in 20 per cent.

Andrews and Braestrup,[29] in 1933, tested the thighs of 24 persons, using a field 7.5 cm. in diameter, with unfiltered radiation and a half value layer of 0.58 mm. of aluminum and also with filtered radiation and a half value layer of 5 mm. of aluminum. They observed that 400 r consistently produced within a few days a pale pink reaction which persisted for about two weeks and that the reaction was apparently slightly less intense with the filtered radiation. The fact that the reaction was slightly less intense with filtered radiation obviously indicates that the reaction to the unfiltered radiation was not a threshold reaction, else there could have been no reaction of less intensity; this illustrates the value of the cutoff point provided by a threshold criterion. They mentioned that Glocker, Hayer and Jungling, using small fields (1.5 by 1.5 cm.) and two different qualities of radiation, had found that the softer radiation caused a more pronounced cutaneous reaction when small doses were used but that when large doses were used no consistent biologic differences between the two qualities of radiation could be noted. They also said that with larger fields Meyer and Glasser had found considerable differences in the reaction with different qualities of radiation.

Pape [30] pointed out that there were four factors involved in determining cutaneous reactions under various conditions of radiation: (*a*) total dose, (*b*) roentgens per minute, (*c*) length of treatment and (*d*) number of partial doses. These could be described as dose, intensity and degree of protraction. These factors are well known in practical therapy, but for the purposes of determining a standard only doses given at a single sitting with intensities in the range in use in practice can be considered.

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28. Duffy, J. J.; McNattin, R. F.; Copeland, M. M., and Quimby, E. H.: Relative Effects Produced by 200 KV. Roentgen Rays, 700 KV. Roentgen Rays and Gamma Rays: V. Comparison Based on Production of Erythema on Human Skin, Am. J. Roentgenol. **29**:343, 1933.

29. Andrews, G. C., and Braestrup, C. B.: Skin Erythema Dose in Terms of Roentgens in Superficial Therapy, Am. J. Roentgenol. **29**:663 (May) 1933.

30. Pape, R.: Comparison of Skin Reactions Under Various Conditions of Irradiation, Strahlentherapie **48**:73, 1933.

The time-intensity factor and the effect of varying protraction are among the questions which a standard biologic criterion, once established, might help to solve.

MacKee,[31] in 1933, expressed the opinion that 350 r (measured in air) at 100 kilovolts constituted the threshold erythema dose for an area of 1 sq. cm. on the flexor surface of the forearm, on the abdomen or on the inner aspect of the thigh.

Holthusen [32] showed that in order to produce an erythema with low intensities, all other factors remaining constant, a greater total dose was required. Thus, if the intensity were 500 r per minute, an erythema would be produced by 500 r; but if the intensity were only 5 r per minute, as much as 1,300 r was necessary. The epilation effect, however, remained constant for a range of intensities varying in the ratio of 1 to 500. He showed that as the intensity, or rate of administration in roentgens per minute, decreased, the separation between erythema and maximum tolerance dose rapidly increased; that is, with higher intensities the tolerance dose was only slightly greater than the erythema dose, while with lower intensities the tolerance dose was much greater than the erythema dose. Certain types of ionization chamber dosimeters in use at that time did not accurately record high intensities, so this might account for part of the enormous discrepancy in reports of this work.

Schwarz and Frank [33] also pointed out that the intensity as well as the total dose should be considered in evaluating the biologic effect of different qualities of radiation. McWhirter [34] found reactions equal for equal doses for intensities ranging from 3.3 to 350 r per minute, although he did not state whether his reaction was a threshold value or was more pronounced. Otto,[35] however, in 1937 observed differences of as much as 300 per cent in the erythema doses at different clinics, but he considered the time-intensity factor to be mainly responsible.

MacKee and Cipollaro [36] reported in 1934 that smaller doses were required when machines and thermionic rectification were used than when

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31. MacKee, C. M., in Glasser, O.: The Science of Radiology, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 293-294 and 298.

32. Holthusen, H., in MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Pre-Cancer: A Practical Monograph, New York, American Journal of Cancer, 1937, pp. 205-206.

33. Schwarz, G., and Frank, A.: Quality of Radiation and the Skin Reaction, Strahlentherapie **50**:145, 1932.

34. McWhirter, R.: Radio-Sensitivity in Relation to the Time Intensity Factor, Brit. J. Radiol. **9**:293, 1936.

35. Otto, E.: Concerning Dosage Questions, Strahlentherapie **58**:361, 1937.

36. MacKee, G. M., and Cipollaro, A. C.: Roentgen Unit in Dermatology, Arch. Dermat. & Syph. **30**:761 (Dec.) 1934.

mechanically rectified machines were used. They observed that with thermionic rectification 212 r produced erythema (pigmentation) within a week or ten days which persisted for about two weeks; with mechanical rectification 266 r produced erythema in most cases. The half value layer apparently was not determined, so this difference, although undoubtedly dependent on the quality of the radiation, cannot be definitely analyzed. The average of eighteen machines was found to be 341 r, and the authors decided on 300 r as their threshold erythema and epilation dose of unfiltered roentgen rays, as that quantity would produce total epilation of the scalp in most cases and also a threshold erythema on an area of 1 sq. inch on the flexor surface of the forearm at about 100 kilovolts, and it was an easy figure to employ for fractional doses. Goldsmith,[37] in 1936, gave 350 r as the dermatologic erythema value, as compared with Wintz's unit skin dose of 600 r. Eller [38] reported the average threshold erythema dose for 80 kilovolts with no filter as 340 r.

Reinhard [39] assumed that the difference in erythema reaction with radiation of different qualities was due to decreased absorption by the skin of hard radiation.

Schwarz and Frank [40] in 1935 repeated a previous observation that the more penetrating the radiation and the greater the target-skin distance, the more injurious the radiation was. This has not been disputed for large doses, but other investigators have not found it to be true for threshold erythema effects, which these authors have apparently not investigated at all.

Meyer [41] pointed out that there was still a controversy over the linking of the physical dose, the cutaneous reaction and the biologic effect. He stated that he still believed there was a difference in the reaction to equal doses with different qualities of radiation and that the secret of biologic response lay in mass absorption; it seems almost axiomatic that radiation which is not absorbed cannot produce any biologic (or other) effect. Quimby, in discussing the paper, said that at Memorial Hospital they had found that different qualities of radiation in equal doses would cause different types of detectors (such as various ionization chambers, erythema reactions, Drosophila eggs and wheat seedlings) to react

37. Goldsmith, W. N.: Recent Advances in Dermatology, London, J. & A. Churchill, Ltd., 1936, p. 444.

38. Eller, J., in Pohle, E. A.: Clinical Roentgen Therapy, Philadelphia, Lea & Febiger, 1938, p. 712.

39. Reinhard, M. D.: Variations in Dosage Dependent upon Wave Length, Am. J. Roentgenol. **31**:538, 1934.

40. Schwarz, G., and Frank, A.: Quality of Radiation and Skin Reaction, Strahlentherapie **54**:83, 1935.

41. Meyer, W. H.: The Relation of Air-Ionization to the Radiation Absorbed and the Effect on Body Tissues, Radiology **25**:198, 1935.

differently. Meyer concluded that there is no advantage and that it is probably harmful to use hard rays for superficial lesions, unless other factors about which little is known play a deciding part in the problem.

Borak [42] discussed regional differences in sensitivity in 1935. He observed weaker reactions for skin and blood vessels adjacent to bone, which could not be explained by physics (absorption and back scatter), and concluded that there must be a difference in sensitivity. He assumed that the probable explanation was that the vessels lying near the bones were subjected to greater pressure than if surrounded by soft tissues, as experiment had shown that when vessels were subjected to compression they and the tissues supplied by them showed decreased sensitivity to radiation.

In 1936 MacComb and Quimby [9] made a series of tests on the recovery of human skin at different intervals after roentgen ray irradiation. They found 69 per cent recovery within twenty-four hours under certain conditions, which agrees with the observations of Reisner, who also determined that the harder the radiation the less the recovery rate.

Kaplan,[43] in 1938, differentiated the erythema dose from the threshold erythema of Quimby and defined it as that dose of radiation which when delivered at one sitting would produce in at least 95 per cent of the subjects a definite reddening of the skin within one week after irradiation, followed by subsequent bronzing but without any permanent injury to the skin.

Andrews [44] defined the erythema dose, in 1938, as the smallest quantity of radiation which would produce a faint pink erythema, the reaction appearing five to seven days after exposure and persisting for one week and then disappearing, generally to be followed by epilation. In general, the duration and intensity of the erythema varied according to the quality of the radiation. If, however, the fields irradiated were small, there was apparently little or no variation in the effect of equal doses of radiation of different qualities. With the quality of radiation usually employed in superficial therapy, unfiltered and with mechanical rectification, the approximate erythema dose was 400 r. When thermionic rectification was used, the erythema dose was approximately 350 r. For 135 kilovolts, with a 3 mm. aluminum filter, the equivalent erythema dose was about 500 r, and for high voltage roentgen therapy at 200 kilovolts, about 600 r.

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42. Borak, J.: Regional Differences in Cutaneous Reactions, Strahlentherapie **52**:74, 1935.

43. Kaplan, I. I.: Radiation Therapy, New York, Oxford University Press, 1938, p. 13.

44. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1938, pp. 49 and 55.

Pohle,[45] in 1938, stated that the mechanism of the constriction and dilation of the blood vessels was not clear, as they responded to such vasomotor stimulants as amyl nitrite and epinephrine; these effects, therefore, could hardly be due to a paralysis of the vasconstrictor nerves, despite the fact that a modification of the irritability of the sympathetic nervous system after irradiation had been demonstrated (e. g., by Swann). The setting free of vasodilator material from damaged cells was not a satisfactory explanation either, because the effect of roentgen rays was seen only where they had actually hit the tissues.

Quimby,[46] in 1938, again drew attention to the fact that the erythema dose differed considerably among the various workers. Some used a full erythema dose, which was the amount of radiation that produced a sharp reddening; others used a threshold erythema dose, which produced a very faint reddening, and still others used a threshold pigmentation dose, which might never produce a reddening but after two weeks or more resulted in a faint bronzing. She said that all these had their drawbacks and that the following points had to be considered: (*a*) the considerable variation in individual susceptibility to radiation; (*b*) the differences in sensitivity between different parts of the body (so that one region had to be selected and always used); (*c*) the size of the area tested, which had to be less than 5 sq. cm. to avoid too great effects from the back scatter; (*d*) the difficulty in determining the degree of reaction with different kinds of normal skin (unless pushed to the point of dermatitis), and (*e*) the need for taking into consideration the texture of the skin, the presence or absence of hair, the natural pigmentation or sunburn and the illumination under which the observations are made. The personal factor is almost as great when observations are made with tintometers as without them. Quimby said that the amount of radiation necessary to produce a sharp erythema reaction varied by more than 50 per cent according to different observers. The threshold erythema dose was subject to less variation, possibly 20 per cent, but the threshold pigmentation dose as previously defined by her could be agreed on by careful observers to within 10 per cent. The threshold erythema dose was in the neighborhood of 15 per cent greater than the threshold pigmentation dose, and the full erythema dose was about 50 per cent greater.

Quimby also pointed out that the effects on the skin did not run parallel to those on Drosophila eggs or to measurements with an ionization chamber. For harder rays, a larger dose measured with the ionization chamber was required to produce a given cutaneous effect. With 100

45. Pohle, E. A.: Clinical Roentgen Therapy, Philadelphia, Lea & Febiger, 1938, p. 116.

46. Quimby, E. H., in MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1938, p. 133.

kilovolts about 300 r (measured in air) produced a threshold erythema, whereas with 200 kilovolts and a 0.5 mm. copper filter about 550 r was required. The threshold pigmentation dose for a small area (less than 5 sq. cm.) at 100 kilovolts was 250 r.

Quimby, Marinelli and Farrow,[47] in 1938, in an article on back scatter, presented tables of the amount of back scatter observed with various qualities of radiation, various depths of underlying tissue and various sizes of the field. These measurements were made with an air-wall thimble chamber and with the Failla extrapolation chamber and showed a maximum back scatter for an area of 5 sq. cm. of 11 per cent with a half value layer of 1.0 mm. of aluminum and of 15 per cent with a half value layer of 0.5 mm. of copper, although in the former case the value was for a minimum depth of tissue of 6 cm. and in the latter 15 cm. (for thin sections it was the same in the two instances). They found no significant difference in the back scatter if the target-skin distance was changed from 30 to 60 cm. for soft rays or from 40 to 150 cm. for hard rays. It is evident from these data that the size of the field used for erythema tests is important.

Desjardins[48] stated that MacKee dehematized a forearm with an Esmarch bandage and administered an erythema dose of roentgen rays to a small area. The circulation was then restored, and an adjacent area was given a similar dose of roentgen rays. In two weeks the reaction in the dehematized area was distinctly less than that in the normal area. He also stated that Schmidt by employing compression was able to administer two erythema doses without reaction. MacKee demonstrated that previous and subsequent irradiation with ultraviolet rays increased the reaction to the roentgen rays.

Goldsmith,[49] in 1939, in a series of tests on 2 subjects found a difference in sensitivity of almost 50 per cent. In a blond subject his threshold erythema dose was 300 r, while in a subject of medium complexion it was 440 r. He noticed an early erythema within six hours, which persisted and merged into the second wave seven to ten days later.

Laymon and Cumming,[50] in 1939, while performing a series of tests on the effect of roentgen rays on the skin of patients taking arsenic

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47. Quimby, E. H.; Marinelli, L. D., and Farrow, J. H.: A Study of Back-Scatter, Am. J. Roentgenol. **39**:799, 1938.

48. Desjardins, A. U.: Action of X-Rays and Radium on Pathological Tissue, in MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1938, p. 272; Clinical Effect of Roentgen Rays and Radium on the Skin, in MacKee, pp. 312-315.

49. Goldsmith, W. N.: Some Notes on the Biological Determination of the Erythema Dose of X-Rays in r-Units, Brit. J. Dermat. **51**:126, 1939.

50. Laymon, C. W., and Cumming, H.: Sensitiveness of Skin to Roentgen Rays Following Ingestion of Arsenic, Arch. Dermat. & Syph. **39**:518 (March) 1939.

internally, found no material differences in the threshold erythema of blonds or brunets. They obtained a faint erythema in two thirds of their subjects with 375 r in an area 2.5 cm. in diameter on the thigh, using 100 kilovolts. They stated, like Miescher, that dark-skinned persons appeared to react more readily than blonds, at least to small doses. An attempt was made to differentiate erythema from pigmentation by diascopic pressure. They found no essential differences in the reactions of men and women or of dry and oily skins. The administration of arsenic had no apparent influence on pigmentation. There was an increase in the percentage of the subjects showing mild erythema after the administration of inorganic arsenic.

Guy, in the discussion of the paper of Laymon and Cumming, stated that he was able to show a variation in susceptibility to different states of the erythema reaction on a subject's arm and on his own. He found that his own skin was more susceptible to the primary reaction and that of his subject to the later reaction.

MacComb,[51] also in 1939, attempted to determine the threshold erythema dose for fields varying from 0.5 to 5.0 cm. in diameter. He used 12 male subjects and exposed the anterior and lateral surfaces of the thighs, irradiating ten fields on each patient. The factors used were: 100 kilovolts, 5 milliamperes, no filter, 30 cm. target-skin distance and an intensity of 275 r per minute, with a half value layer of 1.0 mm. of aluminum. An erythema reaction was produced by 350 r in 80 per cent of the subjects when fields 0.5, 1.0 and 2.0 cm. in diameter were used. For fields 3.0 and 4.5 cm. in diameter, 280 r produced an erythema reaction (doses apparently were measured in air). He stated that it was impossible to determine a different value for each field, the margin being too narrow for such small fields. Accurate physical measurements showed that among the three smallest fields the number of roentgens per erythema dose varied by only 5 per cent, and the same was true among the two larger fields, but between the average of the smaller and larger group a difference of about 10 per cent was found. He noted that in the treatment of epitheliomas, when fields varying from 0.5 to 5.0 cm. in diameter were used, theoretically 15 per cent more radiation could be given to the smallest than to the largest field, but clinically the dose was found to be twice as much. This is in accord with Belisario's observations on volume and tissue injury in part 2 of this paper.

MacComb mentioned that Reisner emphasized the importance of the fact that when erythema determinations were being made, skin unaccustomed to light should not be compared with skin normally exposed to it and that the anterior surface of the thigh was undoubtedly the best

51. MacComb, W. S.: Low Voltage Roentgen Therapy in Skin Cancer, Am. J. Roentgenol. **41**:437, 1939.

surface for making these tests. Reisner had found that 450 r caused an erythema reaction when he used 75 kilovolts and a half value layer of 0.4 mm. of aluminum on a field 2 by 2 cm. in size. MacComb also stated that Quimby and Copeland had found that it required less radiation (at 200 kilovolts) to produce a threshold reaction on a field 4 by 4 cm. in size on the thigh than on a corresponding field on the forearm.

Schwarz,[52] in 1940, stated, as a result of some experiments with 55 and 95 kilovolt radiation, that the higher voltage rays are more harmful than those of lower voltage. He also noted a difference in sensitivity on different areas of the body and the frequent occurrence of the early erythema reactions; both these observations conform with the results to be reported in part 2 of this paper. Schwarz stated that a homogeneous red early reaction with a dose of 250 r is the rule. Belisario [53] observed that some persons require a larger dose. With regard to a former statement by Schwarz and Frank,[40] attention must again be directed to the fact that 1,000 r was administered to an area of 1 sq. cm. for those tests, which is much greater than a threshold erythema dose, and consequently it is feasible for the harder rays to produce an equal, or even more noticeable, reaction than the softer ones, owing to deeper tissue injury or to greater "volume effect." However, the judgment of degree of redness over so small an area would involve a fairly wide range of individual color perception, to say nothing of the margin of experimental error. If threshold erythema doses are used for the comparison of soft and hard radiation (within practical therapeutic limits), it will invariably be found, within the limits of experimental error, that more roentgens are required for the hard than for the soft rays to produce equal reactions. This would seem to substantiate the assumption that more energy is absorbed in the skin with doses of this size of soft than of hard rays, despite Schwarz's statement to the contrary. Finally, his statement that "the term threshold erythema dose should be abolished as not significant" is not supported by any experimental evidence or proof in this paper or in any other paper that we have seen.

SUMMARY OF DATA ACCUMULATED IN AUSTRALIA, THE UNITED STATES AND GREAT BRITAIN

The data herein presented were collected during a tour by one of us (Belisario) in 1937 to Great Britain and the United States; Australian figures are also included. Some of the standards reported may have been changed since that time, but the figures for the Pacific coast of the

52. Schwarz, G.: X-Ray Quality and Skin Reaction, Brit. J. Dermat. **52**:10, 1940.

53. Belisario, J. C.: The Theshold Erythema Dose of Roentgen Rays: II., to be published.

United States and for Australia are more recent and may be considered as those in use at present.

Statistics for one hundred and twelve roentgen ray machines are included, and all have been checked by the threshold erythema test and correlated in international roentgens. Many of the therapeutists, especially in England, were still relying on pastilles for their physical method of dosage measurement and comparison with clinical manifestations; these could not usefully be included in this summary. Although pastilles were employed more frequently in England than in America, they were rapidly being replaced by ionization instruments.

Thermionic (valve) rectification was the prevailing type in use in Great Britain, mechanical rectification having been almost completely discarded; new shock-proof tubes were commonly employed also. The average peak kilovoltage employed in Great Britain was lower than that used in the United States or in Australia; the intensity in roentgens per minute, measured in air, was also lower in England. The fact that the average number of roentgens corresponding to the threshold erythema dose was highest in Great Britain may possibly be accounted for in part by one of the following considerations: 1. There is inherent filtration in the shock-proof tube. 2. Somewhat more than a threshold erythema reaction was often taken as standard. 3. The rate of administration (intensity) was lower. From the experiments of Belisario,[53] it would appear that the first two factors are of primary importance and that the third one apparently makes no clinical difference within the limits in use in practice.

In the United States most of the machines still had mechanical rectification and non-shock-proof tubes. The peak kilovoltage was almost identical throughout the country, but the milliamperage on the East coast was lower, as in Great Britain. The type of tube in use was mainly the broad focus, universal Coolidge tube, with the only inherent filtration being the thin glass wall. On the West coast there was a tendency to use a greater target-skin distance. The intensity in roentgens per minute, measured in air, was slightly higher on the average on the East coast, but not sufficiently so to be of any significance.

The average number of roentgens required to produce a threshold erythema reaction, shown in the table, is somewhat misleading as to the value commonly employed by the great majority of workers. For example, the general trend on the East coast was to employ 300 r as the standard threshold erythema dose, but several higher values brought the average to 368.6 r. In the Middle West 350 r was the value almost universally used, but several lower values brought the average down. On the West coast the majority of workers used either 300 or 350 r as their standard for threshold erythema production.

The fact that the preponderance of tubes with mechanical rectification in the United States should theoretically tend to increase the number of roentgens required to produce a threshold erythema reaction is counterbalanced to a practical extent by the fact that with Universal type tubes the inherent filtration is, in general, much less than with most shockproof tubes, and consequently the resulting radiation has a lower half value layer. This would tend to result in a lower value than that

Factors of Technic and Number of Roentgens Considered Equivalent to Erythema Dose in Australia, the United States and Great Britain

Item	Australia	United States			Great Britain
		West Coast	Middle West	East Coast	
Type of rectification					
a. Mechanical	10	16	18	16	4
b. Valve	5	4	5	8	26
Type of x-ray tube					
a. Shock-proof	6	3	3	1	18
b. Nonshock-proof	9	17	20	23	12
Kilovolts (peak)					
a. Range	70-130	61-110	80-140	80-112	60-130
b. Average	105	96	95.8	95.6	88
Milliamperes					
a. Range	2-6	3-6	2-6	2-3	2-5
b. Average	4.2	4.5	4.1	2.8	3
Filter					
a. 0.5-1.0 mm. aluminum	6	3	..	..	21
b. No filter	9	17	23	24	9
Target-skin distance, cm.					
a. Range	15-25	18-40.5	20-30	20-25	15-30
b. Average	22	28	24.3	20.25	20.25
Roentgens per minute (in air)					
a. Range	70-340	35-237	52-350	100-248	41-150
b. Average	180.5	150.0	147	169	70
Erythema dose equivalent in roentgens					
a. Range	276-470	216-548	250-400	264-528	330-550
b. Average	385	354	340	368.6	435
Type of dosimeter (number of each in use)	Victoreen (8) Siemens (2) Hammer (3) Mekapion (2)	Victoreen (5) Standard air chamber (by physicist) (15)	Victoreen	Victoreen	Hammer (6) Mekapion (6) Ionognom (5) Siemens (2) Dositron (4) Victoreen (7)

accepted in Great Britain.[1] The higher average kilovoltage would tend to increase the magnitude of the dose necessary, compared with that in England, but only theoretically as far as clinical judgment is concerned, and the same argument holds true as for the question of mechanical rectification just discussed.

The main factor of practical importance which may account for the lower dose corresponding to the *threshold* erythema reaction in the United States appears to be the lack of inherent filtration in the tubes and the consequent lower half value layer. The minor variations in the other factors are not sufficiently great to produce discernible clinical

manifestations. Primarily, however, the higher British value for the *erythema dose* is due to the fact that the criterion of reaction was greater than a *threshold* value.

In Australia the number of values obtainable is small compared with those of the other two countries, as there are relatively fewer dosimeters obtainable, although this lack has decreased during the past two years. Mechanical rectification is used in the ratio of two to one as compared with thermionic rectification, which is, however, gradually replacing the mechanical type. Shock-proof tubes are also gradually replacing the non-shock-proof type. The peak kilovoltage on the average is higher than that used in Great Britain or in the United States and is seen in the table to be 105. The milliamperage is similar to that employed in the Middle West and on the Pacific coast of the United States. The tendency toward the use of higher inherent filtration or the addition of from 0.5 to 1.0 mm. of aluminum is also greater. The target-skin distance used in Australia, on the average, compares closely with that in use elsewhere, with the exception of the West Coast of the United States, where it is greater.

The rate of administration (intensity in roentgens per minute) is highest of all in Australia. The average dose in roentgens for a threshold erythema dose comes next to that found in Great Britain in magnitude. This may possibly be accounted for by the greater tendency to use shock-proof tubes with their higher inherent filtration or by the use of thin aluminum filters; the half value layer, for these reasons, is higher than in the United States.

In Great Britain no less than seven different types of dosimeter were used, and since it was not ascertained whether they had all been compared with a recognized standard, complete accuracy of these values is not assured. Belisario was able to *see* the standard of erythema reaction of only a few of the dermatologists in England who were good enough to supply the required data. Individual judgment of the erythema standard varied considerably. In the United States the "Victoreen" thimble type of ionization chamber is used almost exclusively; this uniformity of measuring device in itself affords more accurate comparison between different workers. In the largest centers in the United States most dermatologists' machines were calibrated by a physicist (sometimes two) with a Victoreen dosimeter which was checked against a standard air chamber. Consequently the accuracy of comparison of different machines was as high in the United States as it is at present possible to obtain. In Los Angeles, and elsewhere in California, all the machines the statistics of which are quoted were calibrated with a portable standard air chamber constructed by one of us (Pugh). In Sydney, Melbourne and Perth, from which centers the Australian figures were compiled, four different types of dosimeter were used. More than half of these Australian

figures were obtained with a Victoreen, however, and of these, five were obtained by Belisario with his own Victoreen dosimeter. This instrument was acquired while Belisario was in the United States, and it was compared with a standard air chamber in Cleveland and again in Los Angeles, by Pugh. When Belisario returned to Australia the dosimeter was compared with the standard air chamber at the University of Sidney (by A. H. Harper, consulting physicist), and the readings were all found to agree. Thus, apparently for the first time, a direct check of the dosage in Australia was obtainable for comparison with that employed in the United States, at least as far as the physical measurements are concerned. This fact adds considerable interest to the matter under consideration, because it leaves no room for the supposition that the measurement in roentgens might be different in Australia and in the United States, and hence the results of Belisario's experiments [53] should be equally applicable in the United States.

A general lack of interest in the clinical testing of the erythema reaction was evident among most of the dermatologists in all three countries. For example, in Great Britain, where the pastille was still widely used, the B tint was often taken as the standard of erythema, whereas when this amount of radiation is applied to a 1 sq. inch area of the skin on the flexor surface of the forearm the reaction is invariably greater than a threshold value. Many of the workers whose machines were calibrated in roentgens were content to take the standard of other authorities without ever checking the threshold erythema reaction themselves. Even in the United States, where the accuracy of calibration in roentgens was highest, the tendency among many dermatologists was to accept the standards of MacKee, Andrews or other authorities, regardless of the fact that their own machines often had different half value layers and other varying factors. In Australia this lack of appreciation of the clinical value to the dermatologist of the determination of the threshold erythema dose was even more decided. It is this factor which primarily prompted Belisario to undertake his experimental program in an endeavor to stimulate more interest in this valuable clinical sign. Another fact which was notable was the comparative rarity with which the half value layer was determined. Even in the data cited this was not obtainable in a number of cases and consequently has been omitted from the table. Since the half value layer is the most reliable method of expressing the quality of the beam of radiation in clinical use, it seems most desirable for it to be given in any set of statistics for any machine. It is particularly desirable for purposes of comparison by workers in different centers.

The average dermatologist in the United States was in general better equipped in the sense of correct calibration of his machine by a physicist than was the average dermatologist in Great Britain or in Australia.

On the other hand, the newer valve-rectified machines and shock-proof tubes were more common in both Australia and Great Britain than in the United States, but this does not compensate for the more accurate dosage measurement in the latter.

A large discrepancy was noted in the standard of erythema reaction in the different centers. For example, although the majority of workers used the flexor surface of the forearm of a young, fair-skinned person, others employed the thigh at different levels or the abdomen of subjects of varying age and complexion. The size of the area tested varied from a circle 1 cm. in diameter up to a field of 4 square inches (25 sq. cm.), although the two sizes most commonly employed were circles 1 cm. or 1 inch (2.5 cm.) in diameter. The standard of redness of the reaction varied from an almost imperceptible, irregular or mottled pink blush to definite red with a sharply demarcated border. The latter type, which was actually more than a threshold erythema reaction, was more prevalent in England, where the B tint of the Sabouraud pastille was taken frequently as the equivalent of the erythema reaction. The almost imperceptible pink blush, often a reaction which could not be reconciled with a threshold erythema reaction owing to the difficulty of its perception, was more in evidence on the American East coast and to a lesser extent in the Middle West and Western centers. In these centers the tendency appeared to be to take a standard set of factors in the region of 90 to 100 kilovolts and about 4 milliamperes and to deliver 300 r, as advocated by one authority. If an erythema reaction was observed in 1 or 2 cases and was not seen in several others, it was still taken as a threshold erythema reaction. There seemed to be few attempts to standardize this reaction by a definite proportion of cases in which it could be produced and correlated with a definite clinical appearance. In other words, most investigators appeared to be more satisfied with a certain set of factors in which a certain number of roentgens was used than with a uniformity of appearance of the reaction which could be duplicated by dermatologists in other centers. Consequently, much of the clinical value which could be attached to the threshold erythema reaction was lost.

While it is admitted that even the standard proposed [58] is not a completely accurate measure of dosage, nevertheless it can give important clinical information to the dermatologist if correlated with the number of roentgens administered. Also, now that it is known with certainty that the measurement in roentgens in practical use in Australia can be accurately correlated with that in the United States, it would be of even greater interest if the standard of the threshold erythema dose could be more accurately gaged in the different centers of the two countries as well.

The average therapeutist, using roentgen rays for high voltage roentgen therapy, as distinct from the dermatologist, is mainly concerned with the erythema dose as an incident during treatment of deep-seated lesions, and consequently it has not the same significance for him as it should have for the dermatologist.

Some workers stated that they considered the epilation dose a more accurate measure of clinical effect than the threshold erythema dose. This will be considered again in part 2 of this paper.

The limits for the threshold erythema dose with Belisario's own mechanically rectified machine have been between 250 and 500 r, whereas 350 r has produced this reaction in 80 per cent of the adult subjects; the factors are: 110 kilovolts, 6 milliamperes, 20 cm. target-skin distance, 360 r per minute (measured in air) with a half value layer of 0.9 mm. of aluminum.

One other point which was particularly noticeable by the lack of its appreciation was the appearance of the early erythema reaction. Extremely few workers knew of its occurrence at all, except that occasionally a so-called "electric" erythema was referred to in a vague manner. This was due again to reliance on textbooks and on the work of others, who stated that the threshold erythema reaction appeared somewhere between the fifth and the twelfth days, and the subjects had not been seen before that time, although the early reaction occurs in as high a proportion of cases as does the secondary or principal erythema reaction.

The prevailing impression gained during the tour, more particularly in the United States, was that the erythema dose was a thing of the past now that more accurate measurements with the ionization chamber were available. An attempt will be made in part 2 to show that a properly standardized threshold erythema dose, in correlation with its value in roentgens, is of infinitely greater importance to the dermatologist than are dosage values in roentgens alone.

CONCLUSIONS

The agreement between the observations of different workers as reported in the literature has been, in the main, remarkable. There is little ambiguity in the records of the appearance and clinical progress of visible cutaneous effects as a result of irradiation by roentgen rays, and it would seem that such unanimity of observation should not be wasted but should be utilized, if possible, as a clinical sign to guide further therapeutic procedures.

Many of the values of the erythema dose in terms of roentgens which have not agreed with the majority have been shown in the preceding pages to be due to either a different criterion of reaction or a different

quality of radiation, or both, and consequently their ultimate clinical importance to the dermatologist is slight.

Belisario's own clinical threshold erythema dose is 350 r for the following factors: 110 kilovolts, 6 milliamperes, 20 cm. skin-target distance, 360 r per minute (measured in air), half value layer 0.9 mm. of aluminum, mechanical rectification, a field 1 cm. in diameter on the upper anterior, usually covered, portion of the thigh.

It seems possible to achieve a more uniform average threshold erythema value by standardizing the criterion and recommending the inclusion of the half value layer as one of the essential factors in reporting the technic. In addition to the fact that many dermatologists are reluctant to change completely from a fractional erythema standard of dosage to roentgens, part 2 of this paper will attempt to show that there may be a distinct clinical advantage to the information obtained by a test of the dose required to evoke a threshold erythema reaction in the individual patient.

Various physicians provided the data necessary for the compilation of the tabular material on the technics and dosages in present use in the United States, England and Australia.

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TUBERCULIN IN DERMATOLOGIC DIAGNOSIS

WITH SPECIAL REFERENCE TO THE PURIFIED PROTEIN DERIVATIVE (P.P.D.)

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Old tuberculin has considerable use in dermatology both as a diagnostic and as a therapeutic agent. It is a substance derived from a glycerin and beef broth culture of tubercle bacilli which have been killed with live steam, filtered and washed. In addition to the active skin-sensitizing principle, it contains variable amounts of glycerin, salts, peptones and metabolic bacterial products. The presence of foreign substances derived from the culture medium, while not impairing the value of tuberculin as a therapeutic agent, gives rise to such variation as to interfere considerably when it is used as a diagnostic agent. This applies particularly to the variable potencies of different batches of tuberculin produced by different firms over a period of years, making impossible exact comparable surveys in different parts of the country at different times.

The studies of Seibert and Lewis [1] have shown that the phenomenon of sensitization to the tubercle bacillus (visceral as well as cutaneous) can be reproduced only by the protein fraction of the tubercle bacillus (tuberculoprotein). In an attempt to overcome the variability of old tuberculin and in order to produce a standard exact tuberculin for diagnostic purposes, numerous attempts have been made in Europe and in the United States, resulting in the production of such refined products as the purified protein derivative (P.P.D.).

This substance, as developed by Seibert and her co-workers,[2] is produced by precipitation with trichloroacetic acid of the protein fraction

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1. (*a*) Lewis, J. H., and Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin, the Anaphylactogenic Action of the Protein from Filtrates of Acid-Fast Bacteria, J. Immunol. **20**:201, 1931. (*b*) Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin: XIV. Local Cutaneous Sensitization (Arthus Phenomenon) Produced in Normal Rabbits and Guinea Pigs by the Protein of Tuberculin, J. Infect. Dis. **51**:383, 1932.

2. (*a*) Seibert, F. B., and Munday, B.: The Chemical Composition of the Active Principle of Tuberculin, a Precipitated, Purified Tuberculin Protein Suitable for the Preparation of a Standard Tuberculin, Am. Rev. Tuberc. **25**:724,

(Footnote continued on next page)

of cultures of three potent heat-killed strains of tubercle bacilli followed by extraction with ether. The bacilli are grown on a special synthetic protein-free culture medium (Dorset [3]). The protein fraction thus precipitated is relatively homogeneous, having a molecular weight of from 2,000 to 4,000, and falls therefore in the class of proteoses or polypeptids. While active as an indicator of allergization to the tubercle bacillus, it has no antigenic properties, hence does not sensitize. Antigenicity can be restored, however, by adsorption with such substances as aluminum hydroxide, which acts as a hapten. Purified protein derivative is marketed in measured amounts as crystals incorporated in beta lactose and is supplied in rubber-capped glass vials with a separate vial of a sterile buffered diluent in the package. Depending on the number of tests to be made, packages containing material for as few as five or as many as a hundred tests are supplied. The product comes in two strengths, the first test dilution of 0.00002 mg. and the second of 0.005 mg. In the undiluted form it keeps almost indefinitely. It is diluted at the time of use, obviating the keeping of diluted tuberculin, which is notoriously unstable, especially when contaminated with bacteria, and permitting the preparation of accurate small amounts of tuberculin at the time of the test. The diluted substance maintains its potency for about one week at ice box temperature, according to the recommendations of its originators. I have noted, however, in numerous comparable tests with fresh and with older dilutions, that little difference in reaction intensity was obtained with dilutions even 3 to 4 months old.

While tuberculin field surveys [4] have amply demonstrated the accuracy and value of purified protein derivative, which has been designated as the standard tuberculin by the National Tuberculosis Association, doubt has been expressed from time to time by various dermatologists and allergists as to its accuracy when compared with old tuberculin in dermatologic diagnosis. For this reason the present study was undertaken.

Seventy-nine patients with a wide variety of dermatoses, comprising age groups from 10 to 75 years, were subjected to a total of one hundred and nine parallel tests with purified protein derivative and

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1932. (*b*) Seibert, F. B.: The Isolation and Properties of the Purified Protein Derivative of Tuberculin, ibid. **25**:713, 1932. (*c*) Seibert, F. B.; Aronson, J. D.; Reichel, J.; Clark, L. T., and Long, E. R.: A Standardized Tuberculin for Uniformity in Diagnosis and Epidemiology, ibid. **30**:707, 1934.

3. Dorset, M.: A Comparison of Koch's O.T. with a New Synthetic Medium Tuberculin, J. Am. Vet. M. A. **84**:439, 1934.

4. Long, E. R.; Aronson, J. D., and Seibert, F. B.: Tuberculin Surveys with the Purified Protein Derivative, Am. Rev. Tuberc. **30**:733, 1934.

graded freshly prepared dilutions of a potent old tuberculin (Gilliland). Separate, labeled syringes were used for each concentration and for each type of tuberculin.

The procedure used was as follows: After eliminating by pretesting with a dilution of 1:1,000,000 (0.0001 mg.) of old tuberculin patients with tuberculin hypersensitivity (tuberculids or lupus erythematosus), the first test dose of 0.00002 mg. of purified protein derivative in 0.1 cc. of buffered saline solution was injected intradermally into the forearm in the usual fashion for the Mantoux test. At the same time 0.1 cc. of a 1:100,000 (0.001 mg.) and of a 1:10,000 (0.01 mg.) dilution of old tuberculin (Gilliland) was injected into the other forearm. The reactions were read in forty-eight hours, measured according to length, width and height of papule and erythema and then recorded as negative, doubtful or 1, 2, 3 or 4 plus, following the classification suggested by Aronson for tuberculosis field work.[5] If no

TABLE 1.—*Results of Parallel Tests with Purified Protein Derivative and with Various Dilutions of Old Tuberculin*

Test Dose of Purified Protein Derivative	Total Number of Patients Tested	Positive Reactors	Negative Reactors	Dilution of Old Tuberculin with Which Reaction Was Obtained				
				1,000,000	100,000	10,000	1,000	100
First	63	35	..	4	16	15	..	..
			28	0	0	7	..	..
Second	41	25	..	0	0	8	16	1
			16	0	0	0	1	1 (doubtful)

reaction occurred after forty-eight hours to the first group of tests, the second test dose of purified protein derivative (0.005 mg.) was injected together with 0.1 cc. of 1:1,000 (0.1 mg.) and of 1:100 (1 mg.) dilutions of old tuberculin. The reactions were again read and measured in forty-eight hours. All reactions were also read again after a one week interval. A small number of hypersensitive and of anergic patients were tested with higher and lower dilutions respectively than those just mentioned. The results are contained in table 1. In all instances the first positive (threshold) reaction only is recorded, the reaction to the next higher dilution having been negative.

These results confirm the results of comparative tests of other investigators and indicate that the first test dose of 0.00002 mg. of purified protein derivative is equivalent to from 0.002 to 0.001 mg. of old tuberculin (0.1 of a 1:50,000 to 1:100,000 dilution of old tuberculin), the second test dose (250 times the first) equivalent to approximately 1 mg. of old tuberculin (0.1 of a 1:100 dilution).

5. Aronson, J. D.: The Purified Protein Derivative with Special Reference to the Technique of Tuberculin Injections and the Grading of Reactions, Am. Rev. Tuberc. **30**:727, 1934.

LEVELS OF TUBERCULIN SENSITIVITY IN VARIOUS DERMATOSES

Although in an isolated case of a tuberculous dermatosis the reaction to a given dose of tuberculin cannot be relied on as a diagnostic measure, in general certain types of dermatoses fall into one of several groups, as has been shown by the classic studies of Martenstein and Noll [6] and, more recently, of Bonnevie and With.[7] The results of these statistical surveys are summarized in table 2. The concentration of tuberculin is expressed in terms of dilutions in column 1, in milligrams in column 2 and in the corresponding logarithms of the dilution in column 3 (for example, a 1:1,000 dilution is a dilution of $1:10^3$, or log 3). For the sake of simplicity in tabulation this last method of recording is used in the summary (table 3).

TABLE 2.—*Reactions to Tuberculin in Patients with Tuberculous Dermatoses*

	Old Tuberculin				
	Dilution	Milligrams	Logarithm	Martenstein and Noll [6]	Bonnevie and With [7]
Hyperergic	1:10,000,000	1/100,000	7	Lichen scrofulosorum Rosaceaform tuberculid Papulonecrotic tuberculid (20 per cent of cases)	Rosaceaform tuberculid Papulonecrotic tuberculid
	1:1,000,000	1/10,000	6		
	1:100,000	1/1,000	5		Lupus erythematosus and active tuberculosis Erythema induratum
Normergic	1:10,000	1/100	4	Papulonecrotic tuberculid (80 per cent) Lupus vulgaris, lupus erythematosus	Darier-Roussy sarcoid
	1:1,000	1/10	3	Lupus miliaris disseminatus, erythema induratum	Lupus erythematosus (50 per cent) Lupus vulgaris, scrofuloderma
	1:100	1	2	Sarcoid (33 per cent)	Pulmonary and visceral tuberculosis
	1:10	10	1	Sarcoid (66 per cent)	Sarcoid
Anergic	No reaction	No reaction	0		

In substance there is good agreement in the observations of both groups of investigators. Bonnevie and With found, however, a preponderance of hypersensitivity in patients with papulonecrotic tuberculids, and in their patients with erythema induratum also there was somewhat more sensitivity to tuberculin than in those of Martenstein and Noll. Bonnevie and With stressed the fact that if visceral tubercu-

6. Martenstein, H., and Noll, R.: Statistische Untersuchungen über die Tuberkulinreaktion, Arch. f. Dermat. u. Syph. **158**:409, 1929.

7. Bonnevie, P., and With, T. K.: Quantitative Untersuchungen zur Tuberkulinreaktion (mit der graduirten Intrakutanmethodik) bei verschiedenen Formen von Hauttuberkulose und Tuberkuliden, bzw. bei tuberkuloseverdächtigen Hautkrankheiten, Arch. f. Dermat. u. Syph. **175**:181, 1937.

losis complicates cutaneous tuberculosis (especially lupus vulgaris), there is a tendency toward lessened sensitivity to tuberculin, whereas if active tuberculosis and lupus erythematosus coexist the tendency is toward increased sensitivity.

Table 3 summarizes the results obtained in testing a group of patients with a variety of tuberculous and nontuberculous dermatoses.

TABLE 3.—*Summary of Results of Tuberculin Tests (Threshold Values) in Seventy-Two Patients with Tuberculous and Nontuberculous Dermatoses*

		Logarithm of Tuberculin Dilution							
		Anergic Zone	Hypoergic Zone		Normergic Zone		Hyperergic Zone		
Diagnosis	Number of Patients	0	1	2	3	4	5	6	7
Sarcoidosis									
Pulmonary (only)	1	..	..	1	..	..	..	..	..
Lupus pernio	2	2	..	..	..	..	..	..	..
Miliary lupoid	1	1	..	..	..	..	..	..	..
Disseminated sarcoid									
(White)	1	1	..	..	..	..	..	..	..
(Negro)	7	3	..	2	1	1	..	..	..
Lupus erythematosus									
Discoid	6	..	..	..	1	4	1	..	..
Profundus	2	1	..	..	..	..	..	1	..
Lupus vulgaris	3	..	..	..	..	..	3	..	..
Lupus miliaris faciei	1	..	..	..	..	1	..	..	..
Scrofuloderma	2	..	..	..	..	1	1	..	..
Tuberculosis verrucosa	1	..	..	..	..	..	1	..	..
Papulonecrotic tuberculid	3	..	..	..	..	..	2	..	1
Erythema induratum	7	1	..	..	3	..	2	1	..
Acne									
Vulgaris	4	1	..	..	..	2	1	..	..
Necrotica	1	..	..	..	..	1	..	..	..
Conglobata	2	..	..	2	..	..	..	..	..
Rosacea	5	1	..	..	..	1	1	2	..
Erythema nodosum	3	..	..	..	..	..	3	..	..
Nodulоulcerative syphilid	2	..	..	..	1	1	..	..	..
Dermatitis plus eczema									
Arsenical	3	1	..	..	1	1	..	..	..
Contact	1	..	..	..	1	..	..	..	..
"Allergic"	2	..	..	..	1	..	1	..	..
Diathetic	1	1	..	..	..	..	..	..	..
Seborrheic	1	..	..	..	..	1	..	..	..
Psoriasis guttata	2	..	..	..	..	..	2	..	..
Hydradenitis suppurativa	2	..	..	..	2	..	..	..	..
Streptoderma	3	..	..	..	1	2	..	..	..
Fungous infections									
Tinea capitis	1	..	..	..	1	..	..	..	..
Dermatophytosis	1	..	..	..	1	..	..	..	..
Blastomycosis	1	..	..	..	..	..	..	1	..

COMMENT AND SUMMARY

On the basis of one hundred and nine parallel tests on 79 patients with a wide variety of dermatoses, it can be stated that the purified protein derivative of tuberculin, the active principle of old tuberculin, a chemical fraction of precipitated tuberculoprotein, is equal to freshly prepared dilutions of a potent old tuberculin in detecting sensitized persons. No positive reactions were obtained with this substance in persons in whom they were not also elicited with old tuberculin, and no negative reactions occurred which were not confirmed by old tuberculin. Purified protein derivative is therefore specific.

Because of standard potency, stability, simplicity of preparation and freedom from extraneous protein, purified protein derivative is superior to old tuberculin, with its known factors of variability, tendency toward loss of potency and relatively cumbersome method of dilution. Its superiority as a diagnostic agent has herewith been demonstrated in the dermatologic field, as it has been shown previously and repeatedly in tuberculosis field work. The precipitation and chemical purification to which the product is subjected apparently do not impair its specificity or its sensitivity.

No serious local or focal flares resulted from the use of purified protein derivative in the dilutions marketed, although the first test dose as distributed, being equivalent to 0.001 mg. of old tuberculin, should not be used in patients suspected of being hypersensitive without previous testing with a higher dilution, a principle which applies equally to use of old tuberculin.

Parallel tests with serial dilutions of old tuberculin showed that the first test dose (0.00002 mg.) of purified protein derivative is equivalent to approximately 0.002 mg. of old tuberculin and the second test dose (0.005 mg.) of the derivative is equivalent to approximately 1 mg. of old tuberculin.

A tabular summary of threshold reactions of 72 patients with a variety of dermatoses to graded dilutions of old tuberculin is appended. The results in general coincide well with the large statistical studies of Martenstein and Noll and of Bonnevie and With both for tuberculous and for nontuberculous dermatoses. The determination of the level of tuberculin sensitivity is helpful in the diagnosis of dermatoses of tuberculous origin. A perusal of the results in the group of patients with miscellaneous conditions, however, shows how little of diagnostic import is gained by making routine tuberculin tests of patients with other dermatoses.

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CONTACT DERMATITIS FROM EMETINE HYDROCHLORIDE

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Two patients with contact dermatitis from emetine hydrochloride have recently come under our observation, and on investigation this condition was found in 3 other members of a group of 10 persons working with this substance. Peshkin [1] mentioned its occurrence in 1924, noting "urticaria and itching of hands and forearms from handling emetine solution." Weber [2] cited this reference. Gouriou [3] reported a "zosteriform eruption with urticarious elements in the region of the right femorocutaneous nerve after the subcutaneous injection of emetine hydrochloride in that area." This eruption could have been a contact dermatitis from this drug.

The following cases of typical contact dermatitis in women handling the same batch of emetine hydrochloride in the same plant are reported because of the paucity of references to this substance as a cause of dermatitis.

REPORT OF CASES

CASE 1.—Miss L. W., aged 37, when seen had a dermatitis that had been present one week on the fingers of both hands, in the cubital fossae and on her eyelids. She was employed filling ampules with emetine hydrochloride. The eruption on the right hand, which was used to hold the ampules, was much worse than that on the left. It consisted of vesiculation on an erythematous base on the first three fingers. This patient had filled ampules with this preparation for a few days six months previously, with no ill effects. This last time she had worked continuously with the drug for eleven days. Use of soothing local applications and avoidance of the chemical rendered her free of eruption in a week. Patch tests on her right arm showed only a faint erythema in twenty-four hours, but in forty-eight hours there were markedly positive reactions, with vesiculation, edema and erythema, to both emetine hydrochloride and solution of potassium arsenite U. S. P. The patches were removed after twenty-four hours. Patch tests with other materials elicited no reactions.

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1. Peshkin, M. M.: Bronchial Asthma and Other Allergic Manifestations in Pharmacists, J. A. M. A. **82**:1854 (June 7) 1924.

2. Weber, L. F.: External Causes of Dermatitis: A List of Irritants, Arch. Dermat. & Syph. **35**:1 (Jan.) 1937.

3. Gouriou, E.: Zosteriform Eruption with Urticarious Elements in Territory of Right Femorocutaneous Nerve After Subcutaneous Injection of Emetine Hydrochloride in That Region: Case, Bull. Soc. path. exot. **31**:658, 1938.

CASE 2.—Miss A. G., aged 27, had a history and course much the same as those of Miss L. W. (case 1). She had a dermatitis of the fingers, cubital fossae and entire face. This soon subsided under soothing local treatment. She had been filling ampules with emetine hydrochloride for four days when the eruption first appeared. This was the first time, to the best of her knowledge, that she had handled this drug. Patch tests on the forearm elicited only a mild erythema with emetine hydrochloride and nothing at the other sites in twenty-four hours after their application. In forty-eight hours an intense vesicular reaction was present from emetine hydrochloride and a much weaker reaction was present from solution of potassium arsenite U. S. P. These patch tests were also removed after twenty-four hours. Patch tests with other materials elicited no reactions.

Investigation revealed that the employer, head of a large pharmaceutical company, had a tremendous order for emetine hydrochloride, which is ordinarily not in great demand in this country. Ten women who were regularly employed in other departments were put to work filling ampules with this drug and kept at it continuously for eleven days, or until the dermatitis developed. Two others washed and dried ampules in the same room, and, while they did not fill ampules, they had some contact with containers, table tops and other objects in contact with the drug.

We saw only the 2 patients whose histories are described during the acute attack, but we were told that 3 others of the group of 10 actually employed filling the ampules had a dermatitis of the hands, face and neck. One of these also had inflammation of the nasal mucous membrane with oozing and crusting. All these conditions cleared when the subjects were removed from contact with the emetine hydrochloride. Hence, 5 of 10 persons working with this drug had a dermatitis.

All of the 12 women employed in this department were subsequently given patch tests with arsenic trioxide (1 per cent), solution of potassium arsenite U. S. P., fluidextract of ipecac and the 4 per cent solution of emetine hydrochloride handled by them. Positive reactions were seen only after forty-eight hours, though all the patches were removed in twenty-four hours. All of the 5 women who gave a history of dermatitis during the time of handling the drug exhibited definite, positive reactions to patch tests with both the ipecac and the emetine hydrochloride. All but 1 of the 7 who did not have dermatitis had no reactions. This woman was one of the 2 who cleaned the ampules. Her test site showed only a mild erythema. She may now be hypersensitive to the chemical. Two of the women had handled this chemical for a few days six months previously with no ill effects, and in both of them a dermatitis developed on this exposure. Their hypersensitivity may have developed during this interim.

At the time of the second series of tests on 1 patient (case 1), she again had a reaction to solution of potassium arsenite U. S. P., as well as to the arsenic trioxide. This reaction to solution of potassium

arsenite U. S. P. was about half the intensity of that seen at the time of her dermatitis due to emetine hydrochloride. She had previously handled arsenicals on several occasions.

The second patient (case 2) when tested the second time showed only a mild erythema to solution of potassium arsenite U. S. P. and no reaction to arsenic trioxide. None of the other 10 women tested showed reaction to either solution of potassium arsenite U. S. P. or arsenic trioxide.

There was less than 1 part in 100,000 of arsenic in the emetine hydrochloride powder from which the 4 per cent solution was made for filling ampules.

COMMENT

Apparently emetine hydrochloride would be a more common cause of contact dermatitis were contact with it more often experienced. A 50 per cent incidence puts this substance in the class of a fairly common sensitizing agent.

The necessity for forty-eight hours to elapse between the application of the test patches and the appearance of the intense reaction again reemphasizes the necessity for observing patch test sites at longer intervals than twenty-four hours. This delayed reaction has been observed with many substances. One would have been grossly misled by interpreting the results of these tests at the time the patches were removed, since the reactions were then all negative.

SUMMARY AND CONCLUSIONS

1. Emetine hydrochloride is a common cause of contact dermatitis in persons exposed to it. In 5 of 10 persons filling ampules with it an eruption developed.

2. The importance of observing patch test sites for periods longer than twenty-four hours is reemphasized.

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EXTERNAL CONTACT WITH MONOETHYL ETHER OF DIETHYLENE GLYCOL (CARBITOL SOLVENT)

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The monoethyl ether of diethylene glycol, often known by the trade name of carbitol solvent, has been found technically suitable for the preparation of cosmetic emulsions, lotions and solutions for external application. This ether is said to be undesirable in products for internal administration,[1] but it appears that nothing has been published bearing on the safety of its external uses. The present paper is intended to fill the need for information respecting the local action of the chemical on the skin of animals and of human beings.

Technical considerations not pertinent to this article indicate that most cutaneous contact would be with preparations containing from 5 to 10 per cent of the material, and now it seems unlikely that a concentration as great as 25 per cent would often be encountered. In order to exceed the probable human exposure and thus to allow maximum opportunity for injury, 50 and 70 per cent aqueous solutions of the commercial grade were studied on animal skin, and the undiluted material was applied to human skin. Glycerin U. S. P. was included in the study because it is a widely used ingredient of somewhat similar characteristics, frequently contacting human skin.

IRRITATION OF MUCOUS MEMBRANE

We compared the effect of the monoethyl ether of diethylene glycol on mucous membrane with that of glycerin by instillation of dilutions into the conjunctival sacs of albino rabbits. Solutions were made with an 0.85 per cent solution of sodium chloride to avoid the effect of hypotonicity. We used only normal rabbits the lids of whose two eyes were initially identical in appearance and without congestion.

From the Mellon Institute (Dr. Smyth and Dr. Carpenter).

1. Laug, E. P.; Calvery, H. O.; Morris, H. J., and Woodard, G.: The Toxicology of Some Glycols and Derivatives, J. Indust. Hyg. & Toxicol. **21**:173-201 (May) 1939.

Practically simultaneously 0.5 cc. of a test solution was placed in one eye and the same volume of saline solution in the other eye of the same rabbit. At several time intervals later the lower lids were carefully studied by gently pulling them out so that both could be seen at once on looking down at the head. The appearance of the lid treated with saline solution was taken as normal, and a decision was reached as to whether or not the tested lid was more congested or injected than the control. In this way no quantitative estimates of the degree of congestion were made, and the results were found to be uniform from day to day.

We tested a total of 54 pairs of eyes with different concentrations of the ether and with glycerin. The inflammatory reactions seen were, first, an injection of the capillaries, later followed by congestion. No solution used was sufficiently irritating to cause edema, to produce an escharotic reaction or to yield congestion persisting for twenty-four hours. The results are summarized in table 1.

TABLE 1.—*Irritation of Mucous Membrane, as Measured by Congestion of Eyelids of Rabbits*

Symptom	Least Concentration (per Cent) Producing Symptom	
	Carbitol Solvent	Glycerin U. S. P.
Inflammation for 5 minutes	8	1
Inflammation for 10 minutes	10	1
Inflammation for 30 minutes	12	4
Inflammation for 60 minutes	>30	10
Discomfort (blinking)	20	4
Pain (rubbing eye)	25	6

It is clear from these observations that dilute solutions of carbitol solvent are only slightly irritating to mucous membrane. In view of the results, one might credit emollient properties resembling those of glycerin to dilute solutions of the material.

IRRITATION OF RABBIT SKIN AND WOUNDS

Previous laboratory tests involving three and four day continuous poulticed applications indicated to us that intact animal skin is not injured by single contacts with the solvent. Accordingly, tests were made on more delicate tissue exposed by shallow wounds on rabbits. The first tests were made on minor wounds.

We epilated the flanks of 3 rabbits with a paste of strontium sulfide and zinc oxide. One day later wounds 3 cm. square, made by crossed razor blade cuts into the cutis, one wound on each flank, were at once covered with layers of cotton 1 cm. thick and 7.5 cm. square saturated with a test solution. Until healing was complete the poultices were kept

on the wounds and were replaced daily. Comparisons were made of the two flanks of each rabbit.

In this manner we compared the effects of 50 per cent and 70 per cent aqueous solutions of the monoethyl ether of diethylene glycol and of glycerin, as well as the action of 50 per cent solutions and water. All wounds healed in three or four days, with no consistent difference in rate attributable to the fluids which were compared. Formation of scar tissue was apparently complete in four to six days. The scar from a wound treated with carbitol solvent was thin and narrow without deformity from contraction; its size was the same as that of the original wound. The other scars were thick and wide and contracted to about half the areas of the original wounds. During healing this contraction was apparent as thickened edges along the cuts. The edges of the wounds treated with the solvent were not thickened. There was no injury

TABLE 2.—*Relative Irritation of Tissue, as Estimated by Healing of Wounds on Rabbit Flanks*

Solution Used in Treatment	Wounds Treated	Average Healing Time, in Days	Range of Healing Time, in Days, for Individual Wounds
50 per cent carbitol	4	11.5	8 - 15
None	2	12.5	11 - 14
0.85 per cent sodium chloride	4	13.5	9 - 15
70 per cent carbitol	6	19.5	18 - 24
50 per cent glycerin	2	20.0	16 - 24
70 per cent glycerin	2	21.5	18 - 25

to the intact skin close to the wounds by the three or four days of contact with the materials.

We concluded that the application of concentrated solutions of carbitol solvent did not interfere with normal healing and therefore did not irritate or otherwise injure exposed dermal tissues or intact rabbit skin during three days of continuous contact. Actually this material allowed the formation of thinner and less objectionable scars than did glycerin or water.

The minor wounds mentioned were few and involved only a few days' contact with the test solutions. To allow more prolonged contact, we made major wounds by excising the epidermal and dermal layers and laying bare the muscular wall of the intestine. These excisions measured about 2.5 by 1.5 cm. where the skin was relaxed. They were similarly poulticed until healed, but one layer of gauze intervened between the tissue and the cotton pad to reduce adhesion. Applications were continued until the scab had sloughed off and only a square millimeter or so of dry red tissue remained, at which time healing was considered complete.

We used 10 rabbits, comparing in duplicate the effect of 50 and 70 per cent solutions of carbitol solvent with that of similar solutions of glycerin and of an 0.85 per cent solution of sodium chloride, as well as comparing a wound treated with a 70 per cent solution of carbitol solvent with an untreated wound.

We kept the skin and wounds wet with test solutions continuously for nine to twenty-three days, the time varying with the rate of healing

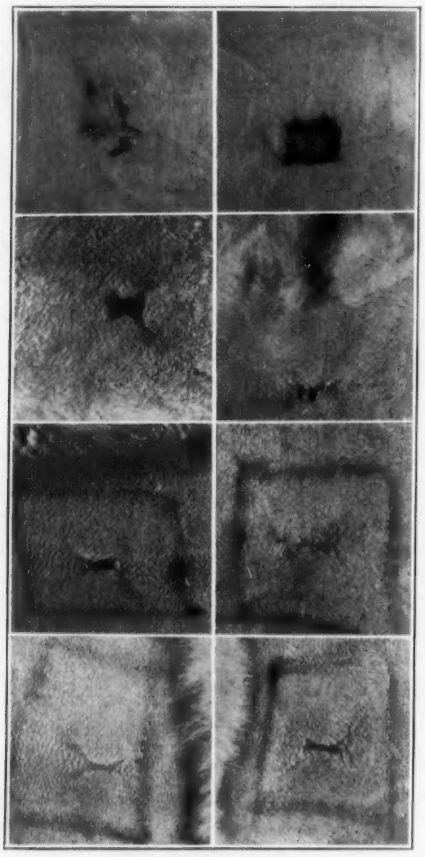

Fig. 1 (rabbit 8875).—Healing of wounds treated with 70 per cent carbitol solvent (left column) and untreated (right column). Top row, fifth day; second row, eighteenth day; third row, twenty-fifth day, and bottom row, thirty-third day. Hair was reclipped for each picture.

of different rabbits. Absorption was of course encouraged by excision of the skin, and it would be anticipated that it was rapid during the first few days before the formation of the scab was complete. During healing, the normal skin adjacent to the wound was not injured, hair continued

to grow to the edge of the scar tissue and there was no evident effect on the health of the rabbits from solvent absorbed into the system. Some of these facts are substantiated by the photographs taken during healing, reproduced in the accompanying illustrations.

All the wounds healed somewhat slowly because no attempt was made to give them optimum treatment. The purpose was rather to compare irritation of various solutions by noting their effects on healing. The significance of the results is limited by the number of wounds studied, but we believe enough were followed to show that solutions of carbitol

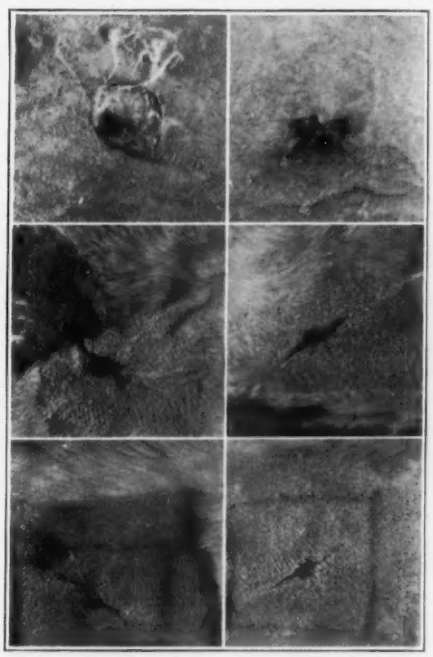

Fig. 2 (rabbit 8719).—Healing of wounds treated with 70 per cent carbitol solvent (left column) and with 0.85 per cent solution of sodium chloride (right column). Top row, fifth day; second row, eighteenth day, and bottom row, twenty-fifth day.

solvent do not retard healing, allow the formation of normal scars and thus are not particularly irritating to exposed dermal and subdermal tissue.

There was no clear evidence that the hygroscopicity of glycerin interfered with healing of wounds, although wounds treated with glycerin did heal slightly more slowly than those in contact with other materials. Carbitol solvent is less hygroscopic than glycerin and would not be expected to injure through dehydration.

PREEXISTING SENSITIVITY OF HUMAN SKIN

We applied undiluted carbitol solvent and glycerin to the skin of 60 persons to detect preexisting allergy. The contact was probably insufficiently prolonged to allow the creation of dermal allergy by sensitization. These persons gently rubbed cotton saturated with the test materials on the inner surface of the wrist for five minutes daily on ten

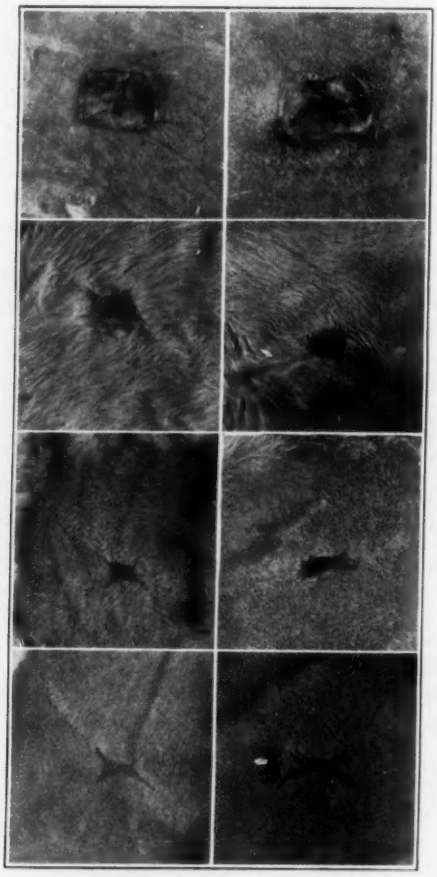

Fig. 3 (rabbit 8717).—Healing of wounds treated with 70 per cent carbitol solvent (left column) and with 70 per cent glycerin (right column). Top row, fifth day; second row, eighteenth day; third row, twenty-fifth day, and bottom row, thirty-third day.

consecutive days. The solvent was applied to the left wrist and glycerin to the right. The skin was not washed for one hour after the rubbing.

All the subjects felt a slight warmth from both the fluids, and most persons reported transient congestion from each material. Three people had congestion or papules persisting several hours or overnight from carbitol solvent, and 6 had somewhat more prolonged reactions from

glycerin. Most of the responses originated at hair follicles, no doubt encouraged by flexing of hair roots from friction, but the mild dermatitis spread to cover uniformly the area rubbed.

The subjects were unselected volunteers from among our colleagues. Their average age was about 25 years, and 60 per cent of them were men. A total of 7 persons had positive reactions, 2 of them to both materials, but only 1 of the reactors was a girl. We realize that 60 persons is a small group from which to draw valid conclusions on the frequency of allergic response, but the indication is strong that fewer persons have cutaneous allergy to carbitol solvent than to glycerin.

SENSITIZATION OF HUMAN SKIN

At a later date we made patch tests on 98 persons to estimate the skin-sensitizing potentialities of this solvent as compared with some other materials.

The subjects were all men college students, averaging about 19 years of age. Applications were made to the back. The compounds were absorbed in ½ inch (1.3 cm.) squares of gauze, covered by 1 inch (2.5 cm.) squares of non-moisture-proof cellophane under a 2 inch (5 cm.) square of water-proof adhesive tape. Initial contact was for seven days; ten days without the patches followed, and the retest application on the same areas of skin lasted for three days.

Carbitol solvent elicited definite reactions in 7 persons, wool fat in 7, theobroma oil in 3, cerate U. S. P. in 9 and ointment U. S. P. in 2. The most severe reaction consisted of decided erythema without papules or obvious edema, and almost every positive response to a test application was less severe than simultaneous response to the adhesive tape.

We conclude that carbitol solvent has no greater skin-sensitizing potentialities than wool fat and cerate U. S. P.

SUMMARY AND CONCLUSIONS

We present experimental results bearing on the effect of external applications of the monoethyl ether of diethylene glycol, often known by the trade name of carbitol solvent.

In the rabbit eye dilute solutions of this solvent are less irritating to the mucous membrane than similar solutions of glycerin.

When concentrated solutions are kept in contact with large wounds in the rabbit flank extending into the muscular fascia, insufficient irritation to the tissue results to retard healing, and during as many as twenty-three days' contact we observed no injury from absorbed material.

We obtained indications that fewer persons have a cutaneous allergy to carbitol solvent than to glycerin.

As a sensitizer of human skin carbitol solvent may be regarded, we believe, as equivalent to wool fat and cerate U. S. P.

TREATMENT OF CUTANEOUS DISEASES WITH RADON OINTMENT AND RADIUM PADS

A PRELIMINARY REPORT

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Radon ointment (radium emanation ointment) was introduced into medical therapy by Strasburger [1] in 1921 and was applied first in dermatology by Uhlmann [2] in 1930 for the treatment of roentgen ray dermatitis and ulcers. Since that time it has been successfully used in many European countries. Happel [3] reported his experience in 1933 and 1934 with the application of radium emanation ointment in the treatment of various dermatoses, and Langer [4] made a report in 1934. In 1937 Brünauer [5] published his results with the use of radon ointment and radium pads in the treatment of cutaneous diseases. Radium pads

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Read before the American Academy of Physical Medicine, New York, April 30, 1941.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. Strasburger, J.: Neuere klinische Erfahrungen bei der Anwendung von Radiumemanation in grösseren Dosen, Allg. med. Central.-Ztg. **90**:289-290 (Dec. 3) 1921; Verbesserte Ausnutzung der Radiumemanation durch Bindung an Fett, Deutsche med. Wchnschr. **49**:1459, 1923; Ueber Radiumemanationstherapie, die Reconvaleszenz, Leipzig, Georg Thieme, 1925, pp. 105-111.

2. Uhlmann, E.: Zur Behandlung der Roentgenschäden der Haut, Dermat. Wchnschr. **91**:1825-1828 (Dec. 13) 1930. Rost, G. A., and Uhlmann, E.: Radiumemanationssalbe zur Behandlung von Roentgenschäden der Haut, Deutsche med. Wchnschr. **58**:655-656 (April 22) 1932. Uhlmann, E., and Schambye, G.: Ueber erfolgreiche Behandlung von Strahlenschäden der Haut, Strahlentherapie **52**:282-293, 1935. Uhlmann, E.: Neue Methoden in der Prophylaxe und Therapie der Roentgenschäden der Haut, Med. Klin. **29**:1649-1651 (Dec. 1) 1933.

3. Happel, P.: Zur Frage der Radiumschwachtherapie, Fortschr. d. Therap. **9**:353-362, 1933; Die Radiumemanations-Salbentherapie, Deutsche med. Wchnschr. **60**:1274-1278 (Aug. 24) 1934.

4. Langer, E.: Radiumemanationswirkung auf die Haut, IV. Internat. Radiol.-Kongr. **2**:330-331, 1934; Die Radiumemanationsbehandlung der Haut, Dermat. Wchnschr. **99**:1264-1267 (Sept. 29) 1934.

5. Brünauer, S. R.: Fall von Lichen ruber planus dispersus geheilt durch "Radiumschwachtherapie" Radonsalbe und Radiummetallkompresse, Wien. klin. Wchnschr. **39**:1198 (Sept. 27) 1935; Zur Strahlenbehandlung der Warzen, Strahlentherapie **29**:255-262, 1928; Zur Anwendung der Radiumschwachtherapie in der Dermatologie, ibid. **58**:83-93, 1937.

were mentioned first in the literature by Heiner,[6] in 1928. Lomholt[7] in 1936 reported his results with radon-containing wax plates.

During the year just passed both forms of radium application were used in the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.[8]

RADON OINTMENT

Radium emanation, or radon, is produced by radium at a constant rate in an amount proportional to the quantity of radium present. Radon, the first product of decay of radium, is also a radioactive substance but in a gaseous state. It can easily be separated from its mother substance by suction into a vacuum. If melted petrolatum is sucked into the same vacuum and thoroughly shaken, a uniform mixture of radon with petrolatum—radon ointment—is created. The concentration of radon ointment, or its power of radiation, can be modified by altering the amount of radium used for the production of radium emanation or the amount of petrolatum, or both; thus one can get any strength desired. The ointment is placed in small collapsible tubes and measured by comparison with a standard preparation and a suitable electroscope.

Radon, an alpha radiator, decays within the petrolatum and produces there the normal products of decay, Ra-A, Ra-B, Ra-C, Ra-C′ etc., emitting alpha, beta and gamma rays like all radium preparations. Hence, radon ointment irradiates the skin with alpha, beta and gamma rays, whereas the usual radon needles, cells and tubes absorb the alpha rays and the soft beta rays within the walls of their containers.

The radioactivity of the radon ointment is defined by electrostatic units or in millicuries, microcuries, etc.

$$1 \text{ millicurie} = 2.75 \times 10^3 \text{ electrostatic units}$$
$$1 \text{ microcurie} = 2.75 \text{ electrostatic units}$$

The amount of applied radiation is defined by millicurie hours, equivalent to the milligram hours.

The radioactivity of the radon ointment is due to the amount of radon present in it. Radon loses its activity with time, according to an exponential law. The half value period of radon is three and eight-tenths days. This means that radon ointment, even in air-tight containers, loses half of its radiation power during about four days; after

6. Heiner, M.: Die Verwendung von Radium-Auflegepräparaten in der Medizin, Med. Klin. **24**:711-712 (May 11) 1928.

7. Lomholt, S.: Alpha and Beta Ray Therapy in Dermatology, Brit. J. Dermat. **48**:567-582 (Nov.) 1936.

8. Radon was prepared in the clinic by Dr. Alois Fischer, who also made the radon ointment and the radium pads.

eight days it contains about a quarter and after twelve days one eighth of the original radioactivity.

The radon ointment is to be applied in such a way that it is pressed from the tube directly on the skin in a layer about 1 mm. thick and covered immediately with oiled silk, which is held in place with adhesive tape as air tight as possible, in order to impede the escape of radon. The amount of radon ointment necessary for treatment depends naturally on the size of the affected area; generally one needs 5 cc. of ointment for covering 1 square decimeter with a layer 1 mm. thick.

RADIUM PAD

A radium pad has a body or carrier of linen or fine-meshed web of bronze or silver on which radium salt is spread uniformly in as fine a layer as possible with a good lacquer. It looks like a piece of oiled silk, is flexible and can be molded to the contour of the body. The pad is wrapped in linen. Since the pad contains radium, its radiation intensity decreases only with the natural disintegration of radium, its strength being reduced to half in one thousand, six hundred and ninety years. Thus, a radium pad keeps its radioactivity practically all the time and is therefore always ready for use, while the radon ointment, losing half of its intensity within about four days, has to be renewed.

The radium pad contains a dose of 0.5 mg. of radium element on a surface of 100 sq. cm., and this amount has proved to be both most effective within a reasonable time and safe, as far as the present state of knowledge seems to indicate. Like the radon ointment, the radium pad gives off alpha, beta and gamma rays, but, in contrast to the ointment, a part of the alpha rays of the pad is filtered away by the lacquer and the linen envelope, and the rest of the alpha rays cannot penetrate deeper into tissue than 0.1 mm.

The radioactivity of the radium pad is defined in milligrams and the amount of the radiation in milligram hours.

RADIATION EFFECT ON TISSUE CAUSED BY RADON OINTMENT, RADIUM PAD AND NORMAL RADIUM PREPARATIONS

About the same radiation effect is achieved if one applies a radium pad eighteen times for twelve hours on an area of 100 sq. cm. or if one administers 5 cc. of radon ointment with 5,000 electrostatic units on a similar area three times within three weeks.

In the first case 0.5 mg. of radium element was applied twelve hours daily for eighteen days, which equaled 108 milligram hours of radiation. In the second case irradiation was started with 5,000 electrostatic units, which equaled 1.81 millicuries, applied to the same area. The amount

of radium emanation, however, decreases, and after seven days 72 per cent of the radon is disintegrated. The quantity of the applied radiation was 173 millicurie hours for one week and 519 millicurie hours for three weeks.[9]

At first sight it seems that 4.8 times more rays are required in order to obtain the same result in treatment with radon ointment as with the radium pad (519:108). One has, however, to realize that a large amount of radium emanation is always lost during the application. As soon as the radon ointment tube is opened radon escapes; much more is lost during the application of the ointment to the skin, and this loss continues until the area treated is bandaged air tight. Furthermore, in spite of air-tight bandaging the emanation cannot be sealed so closely as to prevent a considerable escape of radon. In view of these circumstances the discrepancy in dosage is not great. Now one can understand why many more applications of radon ointment are required and why one observes quicker and surer results with radium pads.

The question arises: How can a relatively small amount of radium spread over an area of 100 sq. cm., as for instance in the case of the radium pad furnished with 0.005 mg. of radium element per square centimeter, cause the noteworthy results observed in the treatment of many cutaneous diseases?

The biologic effect like the physical effect of radiation is considered as proportional to the amount of ray energy absorbed by the exposed object.[10] The alpha and beta rays of the radon ointment as well as those of the radium pad penetrate the skin without hindrance and are absorbed in the first 10 mm. of tissue. The normal radium or radon preparations in containers, to the contrary, radiating gamma rays in principle, keep back alpha and beta rays within the wall of the container. In human tissue gamma rays lose about 90 per cent of their energy after having traversed a distance of 51 cm. A layer of 15.4 cm. absorbs only 50 per cent of the gamma ray energy. In a layer of human tissue between 0.05 and 0.14 cm. thick the total alpha ray energy and 50 per cent of the beta ray energy are already absorbed.

If an average of these values is considered, it is noted that 1 mm. of tissue absorbs all of the alpha ray energy and 50 per cent of the beta ray energy, and 1 cm. absorbs practically all of the alpha and beta ray

9. $D = \frac{A\,(1 - e^{-\lambda t})}{\lambda} = \frac{1.81 \times 0.72}{0.007551} = \frac{1.31}{0.007551} = 173$

D = dose; A = activity at the start; e = basis of the natural logarithm; λ = radioactive constant of radon; t = time.

10. Partially taken from data of Prof. Victor F. Hess, Fordham University.

energy. Therefore, the action of a preparation emitting alpha and beta rays is confined to a region of at most 1 cm. thickness, whereas gamma rays exert their action in a region of 50 cm. thickness. Naturally, the energy absorbed per square centimeter of exposed tissue in the immediate neighborhood of the radium pad or the radon ointment is many times greater for alpha and beta rays, and therefore one can rightly expect that the biologic action of alpha and beta rays in the first centimeter is far greater than that of the gamma rays emitted by normally enclosed radium or radon preparations of the same strength. Within the first centimeter of tissue the alpha and beta ray energy is completely absorbed, while in the same layer only 4.5 per cent of the energy of the gamma rays is absorbed.

The total energy set free by 1 Gm. of radium element and its products of decay is distributed essentially as follows:

	Calory Hours	Per Cent
Alpha and recoil rays	123	89
Beta rays	6	4
Gamma rays	9	7
	138	100

Supposing 10 per cent of the alpha ray energy only may be effective and 90 per cent kept back by the varnish and linen envelope in the case of the radium pad or by the petrolatum in the case of the radon ointment, one can calculate the radium energy set free by the radium pad or the radon ointment in the first centimeter of tissue as follows:

Alpha and recoil rays	8.9 per cent (10 per cent of 89)
Beta rays	4 per cent
Gamma rays	0.3 per cent (4.5 per cent of 7)
	13.2 per cent

This indicates that a radium pad or radon ointment gives off 44 times more energy in the first centimeter of tissue than a radium preparation with the same radium content but normally sealed. From this physical point of view one therefore can expect that the biologic action within the first centimeter of tissue is many times as great as the well known action of gamma rays from needles, cells, tubes or plaques.

Those mathematical calculations agree with my clinical observations. After sufficient irradiation with radon ointment or a radium pad there appears an early erythema and pigmentation and later a stronger erythema. Pigmentation and erythema usually vanish within a few days or weeks under antiphlogistic treatment while the skin desquamates. I believe that no untoward reactions, such as atrophy, telangiectases or

ulcers, will occur if one restricts the radiation of cutaneous diseases with radium pads or radon ointment to a reasonably limited and carefully controlled dosage.

APPLICATION OF RADIUM PAD AND RADON OINTMENT

The application of a radium pad is a clean and simple procedure. Of course only small, up to palm-sized, lesions can be conveniently treated with one pad; the pads are preferable for areas where radon ointment treatment is not suitable, especially for such conditions as lichen simplex chronicus (Vidal) of the neck, in which lesions sometimes extend well onto the scalp. Moreover, there are areas where the application of a radium pad is not possible, for instance the anogenital area, where contact irradiation with radon ointment is preferable.

Before a radium pad is given to the patient he is fully instructed about its application. It is usually applied daily for twelve hours on fourteen to eighteen consecutive days. If three areas are to be treated, the pad has to be changed from one area to the other every eight hours and must be worn accordingly for four days more. The patient is reexamined after one week; after two weeks one has to determine whether or not the treatment should be continued for a few days more. In case a favorable result is not achieved after the first course of treatment, the irradiation should be repeated after a lapse of a month or six weeks in order to give the skin time for recuperation, as is done in roentgen ray treatment. Usually, the first signs of improvement can be noticed after one week. Itching, especially, disappears or diminishes quickly. I was pleased to note that patients using a radium pad adhered to their treatment steadfastly and always returned to the clinic on schedule.

When radon ointment was used, either it was administered in the clinic or one or two tubes of ointment was given to the patient for self application at home. The latter was done only in those cases in which bandaging was difficult or impossible. The ointment should be applied in a 1 mm. thick layer and covered as quickly as possible with an air-tight bandage to prevent the escape of emanation. According to the strength of the ointment, to the way of application and the quality of the bandage, from three (1,000 electrostatic units in 1 cc.) to twenty (100 electrostatic units in 1 cc.) applications are necessary. It is understood that whenever cutaneous lesions are treated in areas where air-tight bandaging is impossible, for instance the anogenital area, one cannot expect the same results as in areas that can be well bandaged.

As a rule, the same radiation effect can be obtained with a radium pad in somewhat less time than with radon ointment.

REPORT OF CASES

In table 1 I have summarized my experience in 85 cases observed in over a year's time. Conditions were reported as "healed" only when clinically excellent results were obtained (disappearance of subjective symptoms, such as itching in pruritus, pain in psoriasis arthropathica and cutaneous manifestations of other diseases) and when no recurrences

TABLE 1.—*Summary of Eighty-Five Cases in Which Treatment with Radon Ointment or Radium Pads Was Given*

Diagnosis	Number of Cases	Condition Healed	Condition Improved	Treatment Discontinued	No Result
Dermatitis papillaris nuchae	1	....	..	1	..
Dermatitis superficialis	1	1	..	..	..
Eczema chronicum lichenificatum	15	9	5	1	..
Keloid	1	....	..	..	1
Kraurosis vulvae	1	1	..	..	..
Lichen planus	6	3	1	1	1
Lichen planus hypertrophicus	2	1	1	..	..
Lichen simplex chronicus (Vidal)	27	18	7	1	1
Naevus flammeus	1	....	1	..	..
Pruritus ani, vulvae or scroti	14	5	3	3	3
Psoriasis	9	2	3	2	2
Psoriasis arthropathica	2	1	1	..	..
Sycosis vulgaris	2	....	1	1	..
Ulcus cruris varicosum	1	....	..	1	..
Roentgen ray dermatitis					
(a) Dermatitis desquamativa	1	....	1	..	..
(b) Dermatitis ulcerosa	1	....	..	1*	..
Total	85	41	24	12	8
Per cent		48.2	28	14.2	9.4

* Treatment was discontinued on account of supervention of epithelioma.

TABLE 2.—*Comparison of Results Obtained by Brünauer and by Isaak*

Cases	Brünauer		Isaak	
	Number	Per Cent	Number	Per Cent
Condition healed	20	55.6	33	57.9
Condition improved	8	22.2	15	26.3
Treatment discontinued	4	11.1	5	8.8
No result	4	11.1	4	7

occurred during a month at the site of the treated lesion. Conditions were labeled "improved" when actual improvement could be noticed clinically and symptomatically. The notation "treatment discontinued" was used when the patient after the start of the treatment either asked for a different treatment or did not repeat the visits to the clinic. "No result" indicates that treatment was abandoned when no improvement could be seen after a certain time.

A comparison of my results with those of Brünauer shows some similarity. Brünauer included among eczematous or eczema-like diseases: eczema chronicum, lichen simplex chronicus (Vidal), eczema

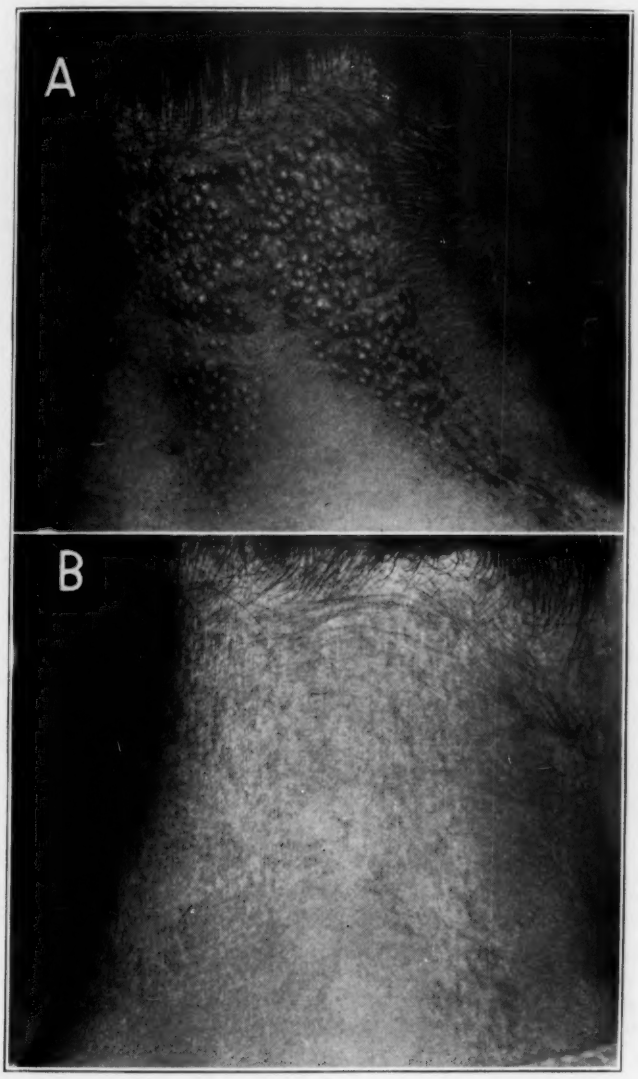

Fig. 1 (case 1).—Lichen simplex chronicus (Vidal): *A*, before treatment; *B*, after treatment with a radium pad.

interdigitale pedum, eczema and pruritus ani, eczema genitale, eczema meatus auditorii externi and neurodermatitis chronica. A comparison of his results with those obtained in my group of the same diseases is shown in table 2.

In 41 cases in which healing was obtained recurrences were observed in 7 (17 per cent), as follows:

1 after one month
2 after two months
2 after three months
1 after four months
1 after six months

CASE 1.—A patient with lichen simplex chronicus (Vidal) of two years' duration was treated with a radium pad. It was applied for eighteen days twelve hours daily. After ten days pigmentation was visible, and after three weeks pruritus and lichenification had disappeared. Reexamination after one-half year showed that the condition remained healed.

CASE 2.—A patient with lichen simplex chronicus (Vidal) of three years' duration had a lesion on the neck which extended well onto the hair line. The lesion was treated with a radium pad for twelve hours on fifteen consecutive days. It healed with pigmentation and erythema. Both disappeared within one month while the skin scaled. There were no recurrences on the hairless area, but twice such lesions appeared within the hair line, which were treated again with a radium pad.

CASE 3.—A patient had lichen simplex chronicus (Vidal) on the neck for six years, which was treated with radon ointment. A large area, 3 by 2 inches (7.5 by 5 cm.), was treated three times at weekly intervals with 3 cc. of ointment containing 700 electrostatic units per cubic centimeter. The condition healed, and it was still healed on reexamination four months later.

CASE 4.—A patient with sycosis vulgaris and roentgen dermatitis of seven years' duration was treated with a radium pad for fourteen days, twelve hours daily. The papular, pustular, erythematous eruptions on the cheeks and upper lip disappeared to a large extent, and the condition improved further under treatment with 30 per cent sulfur in petrolatum.

CASE 5.—A patient with kraurosis vulvae of seven years' duration, showing atrophy and shrinkage of the labia majora, labia minora and clitoris and leukoplakia of the upper part of the vulva, was treated with radon ointment. She received eighteen tubes of ointment containing 100 electrostatic units per cubic centimeter, each tube holding about 7 cc. for self application. Application of this ointment for three months improved the condition so much that the treatment could be interrupted for two months. Another course of radon ointment application, six tubes of ointment containing 500 to 1,000 electrostatic units per cubic centimeter, healed the condition completely. The pruritus and leukoplakia disappeared. A slight recurrence after six months induced the patient to ask for another course of treatment.

CASE 6.—A patient with psoriasis generalisata of five years' duration received treatment with radon ointment to the right leg, which was covered, especially on the extensor surface, with a more than palm-sized lesion of confluent inflammatory scaly patches. After application of eight tubes of radon ointment (100 electrostatic units per cubic centimeter), all the treated lesions had disappeared. Later treatment of lesions on the left leg and right thigh with seven tubes of radon ointment (700 to 1,000 electrostatic units per cubic centimeter) caused only tem-

porary disappearance of the lesions. One month later a general rash of psoriasis spread over the body, leaving free only the right leg and parts of the left leg.

CASE 7.—A patient had generalized psoriasis of eight years' duration, with attacks of psoriasis arthropathica during the time of observation since 1937. The arthritis was always preceded by a severe aggravation of the psoriasis. During the first attack of arthritis the patient was treated with salicylates without result and then with injections of a gold compound (triphal, the sodium salt of aurothiobenzimideazocarboxylic acid). The swollen joints of the left elbow and left hand became painless only after six months. In the second attack the arthritis of the joints of the arms and hands was painful for three months. The patient was again given a gold compound (aurophos, the sodium-gold double salt of an aminoarylphosphinic acid). During the third, fourth and fifth attacks the patient was treated with radium pads, and the pain disappeared each time within three weeks. A pad was applied to every diseased joint for one hundred and eighty to two hundred and sixteen hours. At the same time isolated psoriatic lesions on the forehead, arms and legs were treated with radium pads and vanished promptly after about a hundred and fifty irradiation hours. Figure 2 shows the course of the psoriasis, the relation between psoriasis and arthritis and the duration of each arthritic attack under different treatments.

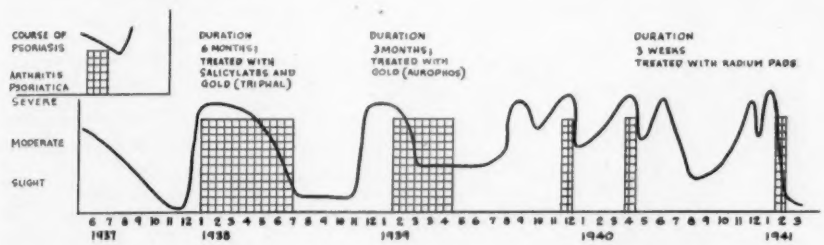

Fig. 2 (case 7).—Psoriasis arthropathica.

CASE 8.—A patient with a clinical diagnosis of eczema marginatum (Hebra) and a histopathologic diagnosis [11] of dermatitis, of over one year's duration, was given all kinds of treatment and roentgen irradiation repeatedly. The condition cleared up after eighteen applications of 2 cc. of radon ointment (100 electrostatic units per cubic centimeter). The condition remained healed.

CASE 9.—A patient with lichen planus hypertrophicus of the leg of one and one-half years' duration was treated without lasting result with roentgen rays (six applications of ¼ skin unit, unfiltered). Irradiation with a radium pad (sixteen days, twelve hours daily) healed the condition. A slight recurrence after two weeks was treated in the same way and was healed again. Reexamination one month later confirmed the healing.

CASE 10.—A patient with lichen planus hypertrophicus of fifteen years' duration was treated without result with numerous injections of bismuth and enesol (mercury salicylarsenate), with roentgen rays and with grenz rays. Radon ointment was applied. First the treatment was restricted to the right leg. After application of one tube of radon ointment (100 electrostatic units per cubic centimeter) daily for eight days the condition improved. One-half year later five tubes of ointment (500 to

11. Report of our histopathologic studies.

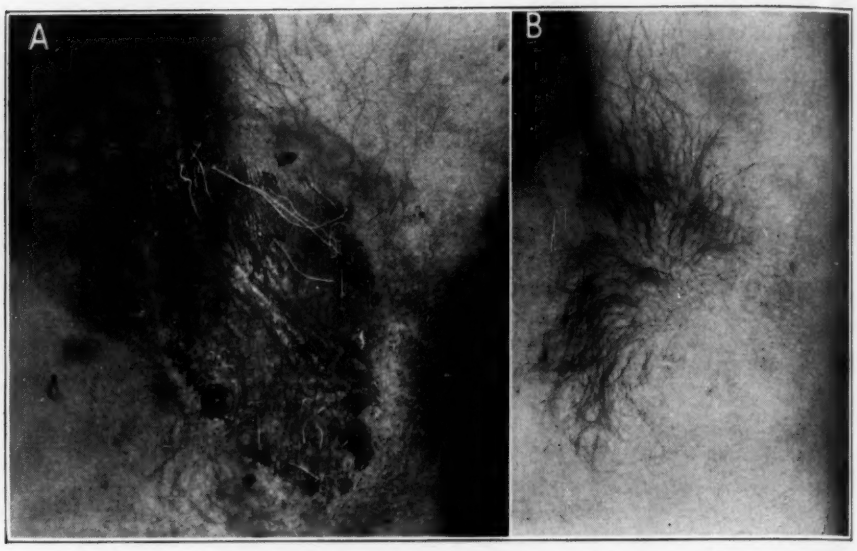

Fig. 3 (case 8).—Dermatitis superficialis: *A*, before treatment; *B*, after treatment with radon ointment.

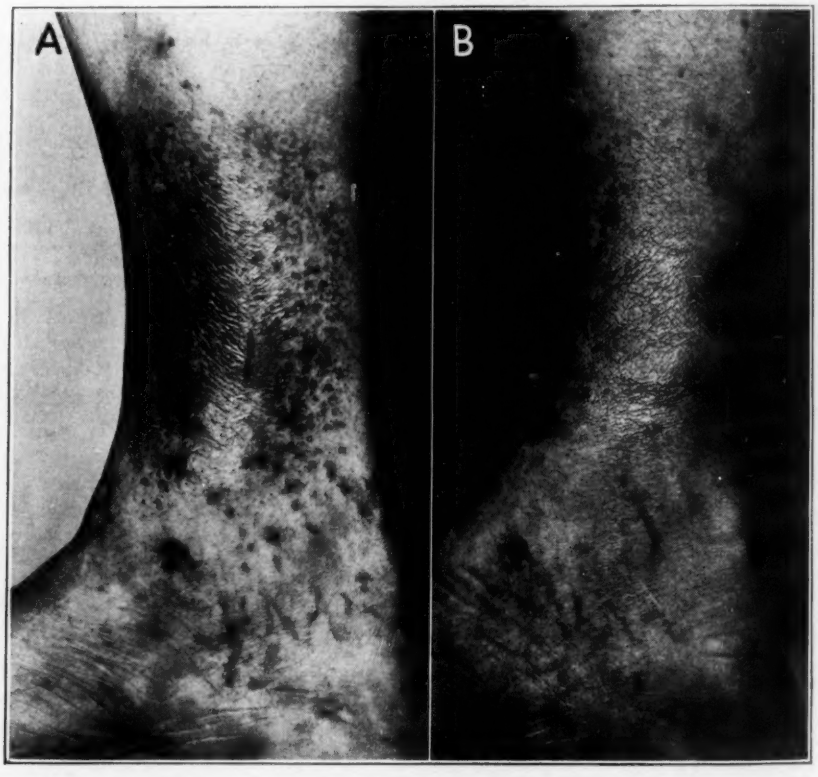

Fig. 4 (case 11).—Eczema chronicum lichenificatum: *A*, before treatment; *B*, after treatment with radon ointment.

1,000 electrostatic units per cubic centimeter) were applied to the same leg. The treatment was followed by erythema and pigmentation, and the lesions cleared up with residual atrophy; only a small area on the lower anterior aspect of the right leg still showed a whitish infiltration. One more application of radon ointment brought entire healing to the right leg, and five tubes of radon ointment (500 to 1,000 electrostatic units per cubic centimeter) applied now to the left leg caused the lesions to disappear. Reexamination one month later showed slight recurrences on both legs.

CASE 11.—A patient with eczema chronicum lichenificatum of five years' duration was treated without result with topical therapy and repeatedly with roentgen rays. Five applications (3 cc.) of radon ointment (200 electrostatic units per cubic centimeter) improved the condition. Three more treatments with an ointment containing 1,000 electrostatic units per cubic centimeter healed the condition, with pigmentation and slight atrophy. Reexamination after two and three months confirmed permanent healing.

CASE 12.—A patient had eczema chronicum lichenificatum of three years' duration. A large lichenified area covered the lower anterior aspect of the right leg and was separated from another area of lichenification on the dorsum of the foot by a narrow bridge of normal skin. In order to find out whether treatment with radon ointment or with roentgen rays would be more successful, the lower lesion on the dorsum of the foot was treated with roentgen rays (three applications of ⅓ skin unit, unfiltered) and the lesion on the leg with seven applications of radon ointment (500 to 1,000 electrostatic units per cubic centimeter). The lesion on the foot did not change much, but the lesion on the leg healed, with pigmentation and erythema. However, recurrence took place, and again treatment with radon ointment was started, this time to both areas (7 cc. of radon ointment containing 1,000 electrostatic units per cubic centimeter). After one week great improvement could be noticed, especially in the lesion on the foot. After the third application of radon ointment all lichenified areas had disappeared.

SUMMARY AND COMMENT

I am able to report excellent results with radon ointment and radium pad treatment in cases of lichen simplex chronicus (Vidal) and other eruptions of localized neurodermatitis. Similar good results were obtained in chronic lichenified eczema, and satisfying results were seen in lichen planus and lichen hypertrophicus. Especially favorable was the effect in the case of eczema marginatum (Hebra), histopathologically a superficial dermatitis; the patient had been unsuccessfully treated for a long time with many kinds of treatment and repeatedly with roentgen rays, and the condition healed finally with radon ointment irradiation. Not less satisfactory was the result in the case of kraurosis vulvae, in which not only the itching disappeared quickly but also the leukoplakia.

I was less satisfied with my results in cases of psoriasis. Although treatment with radium pads seems to have an excellent effect on psoriasis arthropathica, as it has been recommended for the treatment of other forms of arthritis, it should be applied to therapy-resistant isolated

plaques only. I observed new lesions appearing a short time after the involution of irradiated lesions either within the area of the former lesion or on its borders.

The improvement in the case of sycosis vulgaris also proved to be satisfactory.

Among my patients were a number who had been previously treated unsuccessfully with roentgen rays or without lasting benefit. For many of these I succeeded in healing the cutaneous lesion with radon ointment or radium pad irradiation.

Although in more than half of the cases of pruritus ani, vulvae or scroti the condition was healed or improved, the results of treatment in this group were not entirely successful and could well be improved. Thorough examination should exclude such causes as monilia infection, hemorrhoids, fistula, genitourinary disease and irritants before treatment is started.

In 2 cases of lichen simplex chronicus (Vidal) of the neck in which the lesion, which extended well onto the hairy portion of the scalp, was treated with a radium pad, one could see the hairless area of the neck clear up more quickly and more easily than the hairy part. This may be explained by the facts that the hair filters the alpha rays and that the enlarged distance of the radium pad from the skin reduces the effect of the beta rays. This observation teaches that the soft radium rays play a decisive role in the radiation effect emanating from a radium pad.

CONCLUSIONS

It is perhaps too early to draw any conclusions from the relatively little material in this preliminary report and after such a short observation time. One knows that one is dealing especially with alpha and beta radiation when using a radium pad or radon ointment, and one therefore can call this form of treatment "treatment with soft radium rays." I believe that the output of beta and gamma radiation from radium pads and radon ointment is so little that it cannot affect the germinative layer or the capillary system of the skin to such a degree that lasting damage could result. My experience leads me to believe that radon ointment and radium pads are valuable assets in the treatment of diseases of the skin.

Further investigation is necessary to determine the answers to the following questions: Has treatment with soft radium rays any advantages over that with roentgen rays? If so, for which types of eruption? Eventually should a combination of the two forms of radiation be considered? What are the indications for treatment with soft radium rays? Should a strong or a weak radon ointment be used, and which one under which circumstances? Should radon ointment or radium pads

be applied continuously for a certain time or with intermissions? Should late sequelae of irradiation be expected?

NOTE.—Since this paper was submitted for publication 40 more patients have been treated. For the last five months radium pads only have been used. I preferred this treatment for the following reasons: 1. The flexibility of the radium pad permits its application on any area of the body. 2. The radiation output of a radium pad is uniform, thus facilitating exact dosage and preventing overdosage. 3. Better results have been obtained. 4. The treatment time has been shortened. 5. The patients preferred treatment with the radium pads to that with the radon ointment and applied the pads accurately.

45 East Eighty-Fifth Street.

AINHUM ASSOCIATED WITH HYPERKERATOSIS PALMARIS ET PLANTARIS

GERALD A. SPENCER, M.D.
NEW YORK

Ainhum, which was first fully described by da Silva Lima,[1] in 1867, has been observed not only as a clinical entity but also associated with various diseases, e. g., syphilis, leprosy and metabolic diseases. Its association and relation to hyperkeratosis of the palms and soles seem to be of sufficient interest to warrant reporting the following case.

REPORT OF A CASE

G. F., a Negro aged 44, was seen in the dermatologic clinic of Harlem Hospital complaining of a painful growth on the small toe of the right foot. He was born in Texas and had been a resident of New York city for seventeen years. His father was alive. He had three brothers and three sisters, none of whom presented any condition similar to his. The condition began many years before, as soft "corns" on the inner aspects of the small toes. These caused periodic discomfort, which was relieved by cutting and scraping, along with hot foot baths. However, for the past ten years constricting bands around the small toes had become noticeable, and they caused occasional pain along with the appearance of a wartlike growth on the right small toe.

Examination showed a man apparently in good health presenting hyperkeratosis of the palms and soles, more exaggerated on the soles than on the palms. The thickening of the palms and soles had always been present. As a boy he had often amused and amazed his brothers and friends by dancing with pins stuck through his heels and other parts of his soles. On the small toes of both feet there were symmetric constricting circular bands around the first phalanges. On the right toe, where the constriction was more advanced, there was a rotation inward of the distal portion of the toe, thereby causing the inner surface to face upward and the nail to point downward. Also on the inner aspect of this constricting band there was a visible pea-sized crusted lesion overlying an ulceration. The other toes showed no abnormality. Roentgenographic examination of the feet showed rarefaction of the phalanges of the small toes. The Wassermann reaction of the blood was positive. The urine was normal, and mycologic examinations, both direct and cultural, failed to reveal fungi. The physical examination showed no other abnormalities.

From the Department of Dermatology and Syphilology, Harlem Hospital (Service of Drs. S. Irgang and E. R. Alexander).

1. da Silva Lima, J. F.: On Ainhum, Arch. Dermat. **6**:367 (Oct.) 1880.

Fig. 1.—Bilateral constricting bands around the small toes and pea-sized crusted lesion on the right toe.

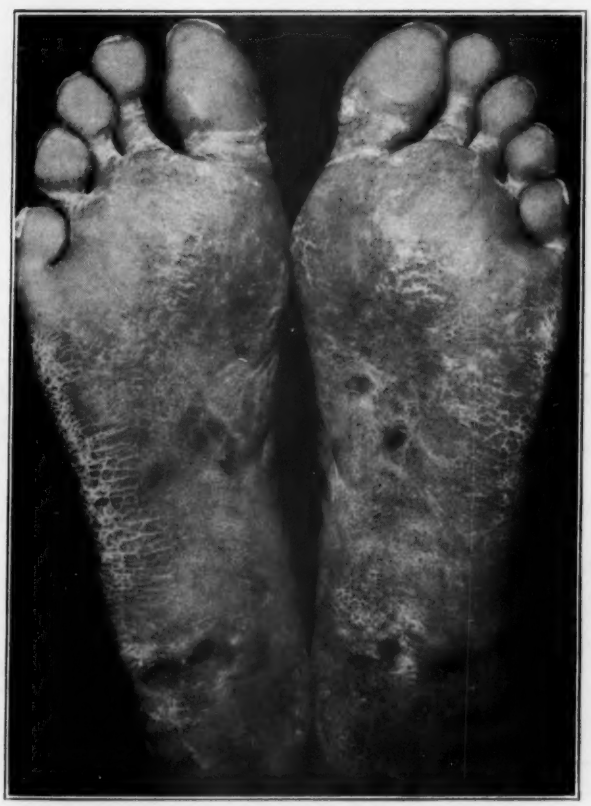

Fig. 2.—Diffuse thickening of the soles.

COMMENT

Since da Silva Lima's description the cases reported of the association of ainhum with other diseases tend to show that it is not an independent disease with a single definite cause but rather only a symptom which may arise in many diseases of varied causes.

Hyde and Montgomery [2] were the first to report cases of ainhum associated with palmar and plantar keratosis, and they expressed the view of the possible relation of scleroderma to ainhum. Unna [3] classified it with keratoma hereditarium mutilans, feeling that ainhum belonged to the group of congenital defects. In 1915 Pawlowskaja-Karyschewa [4] reported several cases in Russia of the association of ainhum with hyperkeratosis palmaris et plantaris.

More recently Wigley,[5] in England, reported ainhum-like constriction of the fingers associated with hyperkeratosis palmaris et plantaris. Grschebin [6] reported a case of ringlike constrictions in a woman with generalized ichthyosis and keratosis palmaris et plantaris. Sutton and Sutton [7] reported 2 cases of ainhum-like lesions of the toes associated with hyperkeratosis palmaris et plantaris. They described a child with ainhum who died of an obscure nervous disorder; the autopsy showed degenerated areas in the cord and sclerosis of the peripheral nerves. In several other case reports ainhum is to be found associated with leprosy, syphilis and metabolic diseases.

In the case presented, from the chronology of events, hyperkeratosis palmaris et plantaris was present from an early age and the stricture followed several years after the onset of the disease. These circumstances make it seem probable that here the ainhum was a sequence of the underlying disease. It is to be noted also that of the cases reported in the

2. Hyde, J. N., and Montgomery, F. H.: A Practical Treatise on Diseases of the Skin, ed. 4, Philadelphia, Lea Bros. & Co., 1897, p. 598.

3. Unna, P. G.: Ueber das Keratoma palmare et plantare hereditarium, Vrtljschr. f. Dermat. **10**:231, 1883.

4. Pawlowskaja-Karyschewa: Case of Scleroderma, Russ. Ztschr. f. Haut- u. Geschlechtskr., 1915; abstracted, J. Cutan. Dis. **36**:133 (Feb.) 1918.

5. Wigley, J. E. M.: Case of Hyperkeratosis Palmaris Plantaris Associated with Ainhum-Like Constriction of Fingers, Brit. J. Dermat. **41**:188 (May) 1929.

6. Grschebin, S.: Observations in Ainhum: Does It Exist as an Independent Disease? Urol. & Cutan. Rev. **50**:98 (Feb.) 1936.

7. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935, p. 624.

United States of ainhum occurring in the Negro there is none recorded of its association with keratosis palmaris et plantaris.

SUMMARY

A case of ainhum associated with hyperkeratosis palmaris et plantaris in a Negro is reported.

The question as to whether ainhum is a clinical entity is discussed.

2135 Seventh Avenue.

Clinical Notes

UNILATERAL NICKEL DERMATITIS OF THE LEFT FOREARM CAUSED BY ZIPPERS

LEON GOLDMAN, M.D., AND H. L. CLAASSEN, M.D., CINCINNATI

Many locations of nickel dermatitis have been described, but occasionally the dermatitis may be present in an unusual location, unusual because the mode of contact is not seen readily. Nickel dermatitis on the forearm and arms comes usually from nickel-plated watch bands or bracelets or in the working man from the nickel-plating bath. Also the dermatitis may appear on the upper extremities by spread from a nickel dermatitis elsewhere on the body. Recently, we have had the opportunity to observe 2 unusual cases of unilateral nickel dermatitis localized to the left forearm.

The 2 patients were women, one a director of nursing education and one a nurse. Each had suspected that she was sensitive to nickel because of episodes in previous years of mild dermatitis from contact with metal ornaments. Neither patient had had cutaneous tests. Each patient presented an acute relapsing unilateral linear papulovesicular dermatitis on the flexor aspect of the left forearm extending slightly above the wrist to the lower limit of the elbow. Neither patient had had a dermatitis in this area previously. One patient suggested close contact with the zipper on the left side of her dress as a possible cause of her dermatitis. The zipper was metallic, unpainted and covered with a cloth flap, and the same type of zipper was found on the dress of the other patient. Both patients were then tested for sensitivity to nickel, and both were sensitive, reacting severely with local and focal reactions even to the nickel coin test. Bland therapy and changing the zipper dress cleared the condition.

Both patients had worn dresses with metallic zippers for many years without any cutaneous irritation under the zipper or on the forearm. Apparently the cloth flaps of this fastener and other layers of clothing were sufficient to protect the skin. The fact that a dermatitis was able to develop from such "inconstant" contact with the metal along the left side of the dress shows how sensitive to nickel these patients were. The unusually hot and humid season in Cincinnati may have caused better contact with the nickel. This fact of easier irritation of the hot moist skin has been noted before in cases of nickel dermatitis.

Approximately 50 per cent of all zippers made contain nickel, the amount varying from 12 to 18 per cent.

Communications with members of two large manufacturers [1] of slide fasteners (zippers) revealed the information that there have been no complaints of irritation of the skin from the use of these fasteners. This is interesting, since many nickel-sensitive persons do wear zippers. This apparent lack of irritation may be due to the fact that an underflap or flap protects the skin from contact with the metal.

If this rare irritation does occur from nickel slide fasteners, it would be better to change to slide fasteners of plastic materials rather than to depend on painting

From the Department of Dermatology and Syphilology, University of Cincinnati College of Medicine.

1. Bessom, E. A.: Personal communication to the authors. Legat, R. C. Jr.: Personal communication to the authors.

or enameling the zippers or covering them with cloth. The covering may wear off or wear through, and in hypersensitive persons cutaneous irritations may be produced.

SUMMARY

Each of 2 nickel-sensitive women had a unilateral linear dermatitis on the flexor surface of the left forearm. This dermatitis was caused by contact with metal zippers in their dresses.

GRANULOMA PYOGENICUM TREATED WITH SULFATHIAZOLE

Report of a Case

J. Richard Allison, M.D., Columbia, S. C.

Mrs. P. H., aged 40, came to my office on April 9, 1941, complaining of a sore on the upper lip. She stated that it had started as a "small pimple" four weeks previously and had gradually increased in size.

Patient with granuloma pyogenicum before (*A*) and after (*B*) treatment with sulfathiazole.

Examination showed a well circumscribed, slightly elevated soft granulomatous lesion, 2 cm. in diameter. It was situated on the middle of the upper lip. The lesion was covered with a thin crust, which was easily removed; the lesion then bled freely. The surrounding tissue was normal. There was a slight enlargement of the cervical glands. The temperature was 99 F.

The patient was admitted to the hospital for observation during treatment. Sixty grains (4 Gm.) of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) was given every twenty-four hours for four days. The dose was then decreased to 30 grains (2 Gm.) every twenty-four hours for one week. Sulfathiazole powder was applied to the lesion twice daily.

The lesion rapidly improved, and in two weeks it was entirely cured.

COMMENT

A case in which granuloma pyogenicum was cured with sulfathiazole is reported. Since the accepted treatment for this disease is total destruction with electrodesiccation, it is interesting to know that sulfathiazole may prove to be an effective method of treatment.

Medical Building.

PITYRIASIS ROSEA

MILTON S. HARTMAN, M.D., BROOKLYN

The following case is reported because of the unusual location of the herald patch and the presence of lesions on the scalp.

REPORT OF A CASE

M. S., a chemist aged 36, consulted me on Nov. 2, 1941. About four weeks previously a pruritic scaly lesion had appeared on the nape of the neck. This was followed in about four days by lesions on the scalp and the body. Examination revealed a rounded somewhat edematous scaly lesion, the size of a quarter, on the nape of the neck within the hair line. Throughout the scalp were scattered about twelve to fifteen scaly papules, from the size of a pinhead to that of a small pea. On the trunk there were a moderate number of oval scaly macules following the lines of cleavage. The arms and thighs were free of lesions. The eruption was accompanied by moderate pruritus.

One erythema dose of ultraviolet radiation was followed by complete disappearance of all lesions within one week. However, involution might have occurred without this treatment, as five weeks had elapsed since the onset of the eruption.

While lesions of the scalp are occasionally seen in pityriasis rosea, they are present only when the eruption is unusually extensive. The lesions in this case were sparse as compared with those in the average case.

711 Bushwick Avenue.

CONTACT DERMATITIS

Change in Sensitivity

M. H. SAMITZ, M.D., PHILADELPHIA

A case is reported in which change in sensitivity of the skin to allergens took place.

REPORT OF A CASE

Mrs. R. N. presented on March 18, 1941 a typical contact type of dermatitis (erythema, scaling and edema) of the upper eyelids of one month's duration. Patch tests with a hard water soap showed a 4 plus reaction (vesiculation) and with nail polish a 2 plus reaction (erythema and scaling). The patient received roentgen treatment (45 r) to the eyelids on March 18 and 21 and a soothing cream to apply. She was advised to stop the use of the soap and the nail polish. The dermatitis cleared in five days, and the patient remained free of the trouble for seven months.

On November 13 the patient returned showing a recurrence of the contact type of dermatitis of the eyelids. She had been using her nail polish again for three months. A patch test with nail polish on this date elicited no reaction (this was the same polish which had caused a positive reaction previously). At this time I learned that she had been using an eyelash curler every two to three days for a month. A patch test with the rubber in this curler elicited a 4 plus reaction (vesiculation). The administration of fractional doses of roentgen rays, application of a soothing ointment and stopping the use of the curler cured the eruption.

News and Comment

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY: FOURTH ANNUAL MEETING

The fourth annual meeting of the American Academy of Dermatology and Syphilology was held at the Waldorf-Astoria Hotel in New York, Dec. 14 to 18, 1941. The attendance was approximately 675, making it the greatest gathering of dermatologists and syphilologists ever held in the United States.

Special courses in "Histopathology," "Mycology," "X-Ray and Radium Therapy" and "Photography" were held on Monday and Tuesday. Approximately 175 members participated in these special courses. The clinical sessions were held at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Monday and Tuesday afternoons. Each member was allowed to attend three separate, one hour clinics, in addition to examining patients exhibiting rare cutaneous diseases. During the entire four days, from Monday until Thursday inclusive, a continuous scientific program was in progress. There were special three hour symposiums on "Avitaminoses," "Allergy," "Syphilis," "Pharmaceutical Therapeutics" and "The Physiology and Chemistry of the Skin." Special lectures by outstanding men in other fields were those by Yale Kneeland, on "The Sulfonamides," Dr. Cornelius P. Rhoads on "The Chemical Causation of Cancer" and by Dr. Edward Lodholz on two subjects, namely, "The Physiology of Senescence of the Skin" and "The Physiology of Pigmentation." Special lectures by members of the Academy were one by Dr. Bedford Shelmire on "Weed Dermatitis" and one by Dr. Vicente Pardo-Castello on "Diseases of the Nails." The Dermatopathology Round Table was again a distinct success.

Special emphasis was placed on the scientific exhibits this year, and many excellent exhibits were presented.

The annual banquet was held on Wednesday evening, with 422 in attendance.

The total membership of the Academy, including fellows, associates and affiliates, is now approximately 825. Hereafter, applications for membership must be in the hands of the secretary at least six weeks prior to the date of the annual meeting in order to be considered at that meeting. Nonmembers may not attend the annual meeting.

The officers for the past year were: Dr. Richard S. Weiss, president; Dr. John G. Downing, vice president; Dr. Clyde L. Cummer, treasurer, and Dr. Earl D. Osborne, secretary. Terms of the treasurer and secretary continue for another year, and the new officers elected were Dr. George M. MacKee, president, and Dr. Everett S. Fox, vice president.

The fifth annual meeting of the American Academy of Dermatology and Syphilology will be held the second week in January 1943 in Cleveland.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

The written examination will be held in various large cities in the United States on Monday, Nov. 16, 1942. Applications must be received by the secretary by Oct. 5, 1942.

The oral examination will be held in Cleveland on Thursday and Friday, Jan. 14 and 15, 1943. Applications in group A must be received by the secretary by Dec. 7, 1942.

If sufficient applications are filed before March 23, 1942, an examination will be held at Atlantic City, N. J., on June 4 and 5, 1942.

C. Guy Lane, M.D., Secretary
416 Marlborough Street
Boston

THE AMERICAN DERMATOLOGICAL ASSOCIATION AND THE AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

On account of the war, the meeting of the American Dermatological Association to have been held June 1 to 4, 1942 has been canceled.

The meeting of the American Academy of Dermatology and Syphilology to have been held Jan. 17 to 20, 1943 has been postponed.

DEATHS

Dr. Douglass William Montgomery, of San Francisco, died on Dec. 21, 1941.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

ESOPHAGEAL OBSTRUCTION DUE TO GUMMATA OF ESOPHAGUS AND DIAPHRAGM. R. H. KAMPMEIER and EDGAR JONES, Am. J. M. Sc. **201**:539 (April) 1941.

Kampmeier and Jones describe 4 cases of esophageal obstruction, produced in 1 instance by a gumma situated in the esophagus and in 3 instances by gummatous lesions of the diaphragm. They emphasize the thought that in a syphilitic patient an obstructive lesion of the esophagus is perhaps more likely to be carcinomatous than gummatous. Even when caused by syphilis the obstruction may be increased after antisyphilitic treatment.

THE TRIVALENT ARSENICALS IN SYPHILIS: SOME RECENT ADVANCES, COMPARISONS AND EVALUATIONS. JOHN H. STOKES and HERMAN BEERMAN, Am. J. M. Sc. **201**:611 (April) 1941.

Stokes and Beerman provide a complete review of recent advances in the therapeutic application of trivalent arsenicals in syphilis.

FAT TOLERANCE TESTS IN PSORIASIS. EDWARD B. LEWINN and I. ZUGERMAN, Am. J. M. Sc. **201**:703 (May) 1941.

In recent years there has been a growing impression that there is an underlying disturbance in fat metabolism in psoriasis. For this reason LeWinn and Zugerman studied the fat tolerance in patients with psoriasis, using a procedure which closely approximates the average diet. Only 1 patient had a fasting blood cholesterol value above the highest commonly accepted normal level. The degree of rise from fasting to the highest level of blood cholesterol varied from 32 to 108 per cent, the average being 51.4 per cent. In control patients the average level of cholesterol was similar and the degree of rise ranged from 24 to 112 per cent, the average being 62.8 per cent. Since the psoriatic subject showed no significant changes as compared with 13 nonpsoriatic patients acting as controls, the authors conclude that psoriasis is a disease due to conditions existing locally in the skin, though it is possible that a generalized disturbance in fat metabolism may contribute to such local conditions.

SCARLATINIFORM ERYTHEMA WITH SYSTEMIC REACTION FOLLOWING INUNCTION WITH MERCURIAL OINTMENT. OTTO E. BILLO, Am. J. M. Sc. **201**:756 (May) 1941.

Billo describes 8 cases of scarlatiniform erythema with evidences of systemic reaction. In each case the reaction followed inunction with mild mercurial ointment U. S. P. in the treatment of pediculosis, and because of the resultant fever and erythema all the patients were referred to the hospital with a diagnosis of scarlet fever. He points out that there was a temperature of at least 101 F. in all but 1 case and that the character of the rash and of the desquamation alone cannot be relied on in differentiating scarlet fever from these idiosyncratic eruptions.

HUMAN CONSTITUTION AND SYPHILITIC INFECTION. A REVIEW OF THE LITERATURE, A PROJECTED METHOD OF STUDY AND PRELIMINARY RESULTS IN 36 PATIENTS. WILLIAM L. FLEMING and JOSEPH EARLE MOORE, Am. J. M. Sc. **202**:38 (July) 1941.

The authors point out that individual variations in the course of syphilis may be due to variation in the virulence of strains of the infective agent, to the

influence of intercurrent disease or to the defense mechanism of the host ("biologic constitution"). Specific definition of the latter factor might enable the prediction of the outcome of the disease and thus allow real individualization of treatment. They report on studies of three groups of white male patients: (1) with late latent syphilis, (2) with gummatous syphilis and (3) with cardiovascular syphilis or neurosyphilis. They determined the blood group and the horse serum sensitivity and made quantitative Wassermann tests and also Mantoux, Schick and Dick tests. Unfortunately, the material was not such as to allow conclusions to be drawn, and the report merely suggests a method of approach to an interesting problem.

OBSERVATIONS ON THE ORAL ADMINISTRATION OF RAGWEED OIL IN PATIENTS HYPERSENSITIVE TO RAGWEED OIL. J. M. SHELDON and F. BLUMENTHAL, Am. J. M. Sc. **202**:98 (July) 1941.

Sheldon and Blumenthal report the results of attempted desensitization of 16 patients having contact dermatitis typical of ragweed sensitivity. The patients had been given patch tests with various dilutions of ragweed oil in olive oil. Treatment consisted of the daily administration of 1 drop of oil in a dilution which gave a faintly positive reaction to a patch test. Twelve of the 16 patients were satisfactorily controlled by this treatment, which was continued over long periods. The clinical response did not parallel the subsequent reactions to quantitative patch tests except in 2 of the patients.

PERSONS LACKING SWEAT GLANDS. F. WILLIAM SUNDERMAN, Arch. Int. Med. **67**:846 (April) 1941.

Sunderman describes 3 brothers suffering from hereditary ectodermal dysplasia. Their chief complaints were fever and headache when they were exposed to high temperatures. In summer their temperatures showed daily oscillations as great as 3 degrees (F.) or more. In 2 of the patients after thirty minutes' exposure in a hot room the cutaneous temperatures increased to 104 and 102.8 F. and the oral temperatures to 101.4 and 102 F., respectively.

Specimens of skin from the axillas were examined by Dr. F. D. Weidman, who reported a total absence of eccrine glands in both patients. The apocrine forms, however, were highly developed, although the involuntary muscle around them was hypoplastic.

HEMORRHAGIC DIATHESES. LAWRENCE PERLMAN and THEODORE A. FOX, Arch. Int. Med. **68**:112 (July) 1941.

Perlman and Fox classify the hemorrhagic diatheses on the basis of physiologic alterations in the blood and in the vessel walls. In a review of 355 cases they observed that the infectious states accounted for the disease in approximately 50 per cent of the cases, bacterial endocarditis and meningitis being the greatest offenders. In 3 cases bleeding was apparently caused by congenital syphilis.

AN EVALUATION OF METHODS AND MECHANICAL DEVICES USED IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASES. BAYARD T. HORTON, FRANK H. KRUSEN and CHARLES SHEARD, Arch. Phys. Therap. **22**:389 (July) 1941.

On the basis of clinical experience and experiments Horton, Krusen and Sheard do not think that the use of the pavaex machine and the intermittent venous occlusion apparatus is capable of promoting increased blood flow in normal extremities or that such apparatus is of any definite value in the treatment of patients who have peripheral vascular disease. They believe that if one is to use any type of apparatus in treatment for peripheral vascular disease, the best is an oscillating bed.

LYNCH, St. Paul.

SYPHILIS OF THE STOMACH. C. WILLIAMS and P. KIMMELSTIEL, J. A. M. A. **115**:578 (Aug. 24) 1940.

Williams and Kimmelstiel report a case of syphilis of the stomach, the eighth of a series. As in other cases, the site of the involvement was the pylorus. The presenting symptoms usually consist of epigastric pain, vomiting and loss of weight. If the patient is below the cancer age, if the Wassermann reaction is positive and if a roentgenogram reveals a smooth funnel-like or tubelike deformity of the stomach a syphilitic lesion of the stomach is the most likely diagnosis. Medical treatment is not always successful; when it is not, surgical resection is the method of choice.

TREATMENT OF PSORIASIS. J. F. MADDEN, J. A. M. A. **115**:588 (Aug. 24) 1940.

Madden reports the results of various forms of therapy of 112 patients with psoriasis during two years. The following therapeutic agents were investigated: vitamin D, vitamin B_1, vitamin B complex, brewers' yeast, vitamin C, liver extract, diluted hydrochloric acid, estrogenic substance, sulfanilamide, bismuth salicylate and anterior pituitary extract or adrenal cortex extract alone or in combination with one another or in combination with a low fat diet. On the basis of his observations Madden now uses as the treatment of choice a low fat diet plus 1,000 international units of vitamin B_1 daily by mouth, combined with the application of an exfoliating ointment.

CUTANEOUS MANIFESTATION FROM TOBACCO, WITH SPECIAL REFERENCE TO ARSENICAL EXFOLIATIVE DERMATITIS. E. E. BARKSDALE, J. A. M. A. **115**: 672 (Aug. 31) 1940.

Using the Gutzeit test for arsenic, Barksdale analyzed cigarets, cigars, snuff, chewing tobacco and smoking tobacco, purchased in the open market. All samples contained arsenic. Cigaret smoke was shown to contain arsenic in a form which may be taken up by the human body. In each of 8 cases of exfoliating dermatitis the etiologic agent was considered to be arsenic contained in tobacco. Barksdale studied a control series and on the basis of comparison decided that determination of the arsenic content of the blood was of considerable aid in diagnosis.

DERMATITIS: CHAIRMAN'S ADDRESS. J. G. DOWNING, J. A. M. A. **115**:813 (Sept. 7) 1940.

Downing reviews the newer concepts regarding dermatitis and eczema. He stresses particularly the value of careful history taking with emphasis on family history for allergic diseases, time of onset, number of attacks and exposure to known irritants or sensitizing substances. He reports on the results of questionnaires sent to 1,000 workers who had suffered from occupational dermatitis. Replies were received from 212 persons. About 50 per cent were found to be able to resume their normal occupations without suffering a recurrence of the dermatitis. His studies on the prevalence of secondary infection showed that patients with contact dermatitis are no more subject to mycotic infection than patients with normal skin. Downing also calls attention to the possibility of sensitization of the skin from within, chiefly through sensitization to or overdosage of drugs. Prevention is possible in many instances by increased knowledge of potential sensitization, by lawful restriction of marketing of sensitizers, by educating the laity to less self medication and by preaching good personal and industrial hygiene.

AN OUTBREAK OF DERMATITIS FROM NEW RESIN FABRIC FINISHES. L. SCHWARTZ and others, J. A. M. A. **115**:906 (Sept. 14) 1940.

Seemingly separate outbreaks of dermatitis in various states and in Canada were found to have a common cause. The eczematous eruptions appeared after the subjects wore various types of wearing apparel, including pajamas, shorts,

dresses and other cotton, finished materials. The cause of the dermatitis was determined to be the finish of the goods, which was an emulsion of an acid ester gum. Patch tests were used to determine the causal relation. A plea is made for tests on rabbits with any proposed new chemical and for later tests on patients to determine whether the substance is a primary cutaneous irritant or is capable of sensitizing an appreciable percentage of human beings.

DERMATITIS OF THE HANDS IN HOUSEWIVES. J. W. JORDON, F. A. DOLCE and E. D. OSBORNE, J. A. M. A. **115**:1001 (Sept. 21) 1940.

Jordon, Dolce and Osborne stress the importance of soap and cleansers in the causation of vesicular eczema of the backs of the hands in housewives. The condition usually improves in the summer. The disorder is frequently misdiagnosed and badly treated, the chief difficulty being in confusing the condition with dermatophytosis. Beside the usual treatment of avoiding contact with soap and the application of bland preparations, the authors have had good results from the use of alkyl sulfonates as soap substitutes.

DERRIS ROOT DERMATITIS. M. DORNE and T. B. FRIEDMAN, J. A. M. A. **115**:1268 (Oct. 12) 1940.

Dorne and Friedman report the case of a florist's helper aged 27 who had a widespread pruritus and when examined was found to have a discrete papular and pustular eruption on the thighs and legs, in the popliteal spaces and over the sacrum. There was redness in the cubital fossae. Dermographism was present. He had been using an insecticide spray prior to the onset. Patch tests and scratch tests gave negative results. However, intracutaneous tests elicited an extensive reaction to a 1 : 1,000 solution of derris extract, a component of the spray. Circulating antibodies to this substance were demonstrated by passive transfer tests.

SULFANILAMIDE IN THE TREATMENT OF ERYSIPELAS: A CONTROL STUDY. J. A. FOLEY and E. R. YASUNA, J. A. M. A. **115**:1330 (Oct. 19) 1940.

Foley and Yasuna administered sulfanilamide to 80 patients with erysipelas. In comparing the results with those of 80 patients who did not receive the drug, it was noted that for the treated patients the temperature returned to normal two days earlier, the hospital stay was shortened three days, complications were halved and the mortality was a quarter. Two patients treated by sulfanilamide died in uremia, and the authors think it possible that sulfanilamide was responsible.

CANCER OF THE SKIN IN RELATION TO MULTIPLE MALIGNANT GROWTHS. S. WARREN and O. GATES, J. A. M. A. **115**:1705 (Nov. 16) 1940.

On the basis of 1,149 carefully studied cases of cancer of the skin, Warren and Gates conclude that there is no justification for recommending the induction of cancer of the skin to protect against the development of cancer elsewhere. On the contrary, they found that cancer affecting organs other than the skin is more likely to develop in patients with cutaneous cancer than in control patients of the same age. They conclude that cancer of the skin does not protect against the development of cancer elsewhere.

LEWIS, New York.

HETEROLOGOUS TRANSPLANTATION OF MAMMALIAN TUMORS: II. THE TRANSFER OF HUMAN TUMORS TO ALIEN SPECIES. HARRY S. N. GREENE, J. Exper. Med. **73**:475 (April) 1941.

Greene has demonstrated that in certain instances human as well as rabbit tumors can be transplanted to alien species and maintained by serial passage in the foreign host. The tumors consisted of cancers of the breast, uterine fundus,

cervix, colon and tongue. Except for the cancers of the breast, all the tumors were infected after transplantation, and it was necessary to discard the animals. Successful takes resulted in 2 of 4 mammary cancers.

INHERITANCE IN GUINEA PIGS OF THE SUSCEPTIBILITY TO SKIN SENSITIZATION WITH SIMPLE CHEMICAL COMPOUNDS. MERRILL W. CHASE, J. Exper. Med. **73**:711 (June) 1941.

Chase believes that he has demonstrated the existence of variations of a hereditary nature in the capacity for sensitization to poison ivy and to dinitrochlorobenzene. This was done by the controlled breeding of guinea pigs chosen for high or low susceptibility to experimental sensitization.

LYNCH, St. Paul.

THE TREATMENT OF POST-RADIATION NECROSIS BY RADIATION THERAPY. ALBERT EIDINOW, Brit. J. Dermat. **53**:171 (June) 1941.

Postirradiation complications are treated by massive doses of ultraviolet rays at intervals of fourteen days and in the interim by daily exposures to infra-red rays. The same method of treatment with varying doses is used for acute and chronic radiation dermatitis, postirradiation sclerosis and subacute or chronic ulceration. Postirradiation telangiectases are first destroyed by diathermy and then treated with ultraviolet and infra-red rays. The technic of the local ultraviolet irradiation aims at the production of a full erythema or counterirritation effect. The lamp is placed as closely as is practicable to the lesion; the surrounding area is protected, and a dose fifteen to thirty times that necessary to produce an erythema on normal white skin is given. A full blistering reaction should be produced. Postirradiation lesions in the oral regions heal more rapidly than lesions on the skin. A study of 74 cases of postirradiation ulcers showed that in 12 per cent malignant disease had recurred, and the author cautions that ultraviolet rays stimulate activity of malignant cells and accelerate their growth. The article is not illustrated.

A NEW PREPARATION OF METALLIC OXIDES WITH DEHYDRATING AND ANTIPHLOGISTIC EFFECTS ON THE SKIN. HENRY C. SEMON and FRANZ HERRMANN, Brit. J. Dermat. **53**:177 (June) 1941.

The authors recommend for the treatment of subacute dermatitis a new preparation which they call siccolam, containing 24 per cent of zinc oxide, 21 per cent of titanium oxide and 8.5 per cent of colloidal kaolin made into a thick cream with a mixture of glycerin and water, 1 part of glycerin and 2 parts of water. The compound is said to have a high dehydrating capacity and is capable of quickly giving off the fluid abstracted from edematous tissue. The preparation is indicated for all conditions in which the use of fatty preparations are contraindicated.

"PEMPHIGUS SOLITARIUS CICATRISANS." TWISTON DAVIES, Brit. J. Dermat. **53**:187 (June) 1941.

The author describes 7 cases, with regard to which he says: "The complaint is of bullae occurring, usually singly, at intervals varying between two days and two years. The bulla, which is often preceded by an erythematous nodule or ring, is thick-walled and may last several days without the contents becoming turbid. It is succeeded by an ulcer having thickened torpid edges taking many weeks to heal and invariably leaving a scar. The scar is usually conspicuous, sometimes hypertrophic. The lesions occur on skin which is otherwise normal. While they are mostly found on the hands and wrists, they may also occur on parts covered by clothing, and other parts relatively inaccessible to the patients' hands or to sources of accidental trauma. The long intervals between attacks and their unexpectedness are among the reasons why not much investigation has been

attempted. The results of all investigations that have been undertaken so far were negative."

Conditions considered in the differential diagnosis and apparently ruled out were artefact, multiple neurotic gangrene, insect bites, pus infection, virus disease, drug eruption, formes frustes of the pemphigus group and erythema multiforme.

RATTNER, Chicago.

SEARCH FOR BACILLI IN THE BLOOD IN LUPUS VULGARIS DURING BIOLOGIC AND PHYSICAL THERAPY. L. SEMMOLA, Dermosifilografo **15**:653 (Oct.) 1940.

Blood cultures in 28 cases of lupus vulgaris during therapy with radium, diathermocoagulation, ultraviolet rays and vaccine were constantly and repeatedly negative for tubercle bacilli.

SUPPOSED INCOMPATIBILITY BETWEEN ARSPHENAMINE AND SULFANILAMIDE. G. CALETTI, Dermosifilografo **15**:707 (Nov.) 1940.

Experiments in animals and in patients with syphilis and gonorrhea demonstrated that the use of arsphenamine and sulfanilamide in the same subject is well tolerated and effective.

DEXTROSE CONTENT OF THE SKIN AND INTRADERMAL INSULIN THERAPY IN PSORIASIS. A. PANTI, Dermosifilografo **15**:713 (Nov.) 1940.

In 43 cases of psoriasis Panti found an increased quantity of dextrose in the skin while the quantity in the blood was normal.

Intradermal injections of insulin in the lesions of psoriasis caused their involution in a few cases.

INVOLVEMENT OF THE NERVOUS SYSTEM IN BESNIER-BOECK-SCHAUMANN DISEASE. S. QUADRI and G. MARICONDA, Dermosifilografo **16**:213 (April) 1941.

The authors studied a case of benign meningitis. This condition developed in a 5 month old baby and was followed a few days after recovery by a cutaneous nodular eruption which pathologically showed typical Besnier-Boeck-Schaumann disease. Roentgen examination of the hands showed typical cystic osteitis.

THERAPY OF HERPES ZOSTER. F. FIUMICELLI, Dermosifilografo **16**:230 (April) 1941.

Fiumicelli has obtained resolution of the eruption and disappearance of pain within five to fifteen days with from 2 to 4 erythema doses of ultraviolet rays in 17 cases of herpes zoster. The treatment must start at the very beginning of the blister formation and is given every three or four days. The amount must be exactly 1 erythema dose.

SULFANILAMIDE THERAPY IN THREE CASES OF ANTHRAX. T. ANIELLO, Dermosifilografo **16**:271 (May) 1941.

In 3 cases of anthrax Aniello noticed that the administration of sulfanilamide had a favorable effect on the course of the disease. He states, however, that in his opinion the serum is still the most effective method of therapy.

RONCHESE, Providence, R. I.

PRELIMINARY REPORT ON THE TREATMENT OF VENEREAL WARTS WITH THEIR EXTRACTS. J. M. CONDE MUNOZ, Actas dermo-sif. **32**:816 (June) 1941.

The author based his study on the experience of Biberstein in Jadassohn's clinic, who cured 75 per cent of his patients with less than ten injections of an extract of venereal warts.

The substance injected was a suspension of venereal warts, crushed in a mortar and heated at 60 C. for one hour. The doses varied from 0.5 to 1 cc. Three patients with large lesions were treated, 2 of them responding satisfactorily. Injections of distilled water were used in 1 case, as a control, without improvement.

Conde Munoz states that this treatment may be of value for patients with large lesions, surgical removal or destruction of which by physical methods may lead to large scars.

CANIZARES, New York.

TREATMENT OF LUPUS ERYTHEMATOSUS OF THE MOUTH. H. LEICHER, Ztschr. f. Hals-, Nasen- u. Ohrenh. **46**:81, 1939.

After discussing in detail the differential diagnosis of lupus erythematosus, Leicher considers the various methods of treatment, mentioning the use of bismuth, of gold and of potassium iodide, the local application of solid carbon dioxide and roentgen irradiation. He stresses the unsatisfactory results that have been obtained by all of these measures. He reports a series of 4 cases, in 3 of which cures were effected by electrocoagulation of the lesion.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

ERYTHEMA NODOSUM WITH INVOLEMENT OF THE CONJUNCTIVA. E. KISSIN, Vestnik oftal. **16**:506, 1940.

Kissin found only 6 previously reported cases of erythema nodosum of the skin in which the conjunctiva was affected. In all cases bilateral involvement of the conjunctiva was observed. A woman aged 50 complained of general malaise and "blisters" of the skin of both legs and one shoulder of one week's duration; prior to this she had had a sore throat for four days. There were a number of firm, painful nodules on the legs and on the left shoulder. There was a solitary nodule on the temporal side of the conjunctiva of each eye, about 3 mm. from the limbus, at the palpebral fissure. Its diameter was 5 or 6 mm.; it was heavily vascularized, with distinct borders. Bacteriologic examination showed hemolytic streptococci in the throat and conjunctiva and also a great number of leukocytes (pyelitis) in the urine. The ocular and the general symptoms disappeared coincidentally with absorption of the cutaneous lesions.

This benign course of erythema nodosum, despite the severe clinical symptoms, suggests that the disease is allergic. In the case reported, local allergy of the conjuctiva in relation to the hemolytic streptococci is suggested.

O. SITCHEVSKA. [ARCH. OPHTH.]

CLINICAL AND EXPERIMENTAL STUDIES OF FUNGOUS INFECTIONS IN OSAKA AND SURROUNDINGS. H. ANDO, Jap. J. Dermat. & Urol. **47**:62 (Sept.) 1940.

The author examined 12,364 school children and 2,203 young men and patients of the dermatologic clinic of the University of Osaka in regard to fungous infections of the skin. The following essential observations were made: 207 species of different fungi were cultured, namely, 76 of Microsporon japonicum, 7 of Trichophyton violaceum, 7 of Trichophyton glabrum, 5 of Trichophyton asteroides, 97 of Trichophyton purpureum, 13 of Trichophyton interdigitale and 2 of Epidermophyton inguinale.

In culturing the material, disinfection with 0.1 per cent mercury bichloride proved superior to that with alcohol. In 83 per cent of the cases of superficial fungous infection of the scalp the condition was due to M. japonicum. In 1 case of tinea profunda of the scalp there was associated lichen trichophyticus, which has been rarely reported in Japan.

In vesicular and marginated fungous eruptions of the body there was most frequently found T. purpureum. In only 1 case of marginated eczematous tinea there was found T. interdigitale. In pompholyx-like eruptions, T. interdigitale and T. purpureum were cultured. In lesions of the nails only T. purpureum was found.

ANTIPYRINE AND RENAL DAMAGE. S. AOSIMA, Jap. J. Dermat. & Urol. **47**:69 (April) 1940.

Administration of antipyrine to rabbits frequently produced disturbances in renal function. Inhibited elimination of antipyrine in the urine was observed. The author considers renal damage as a possible factor in the causation of antipyrine eruptions.

LYMPHOGRANULOMATOSIS MALIGNA (HODGKIN'S DISEASE). M. IWAMA, Jap. J. Dermat. & Urol. **47**:71 (April) 1940.

The author succeeded in cultivating gram-positive bacilli on Petragnani's medium from gland tissue of a patient with Hodgkin's disease. Inoculation experiments in rabbits were successful. The author considers the gram-positive bacillus as the causative agent of Hodgkin's disease. BLOOM, New York.

DEMENTIA PARALYTICA INFANTILIS ET JUVENILIS. GEORG K. STÜRUP, Ugesk. f. læger **101**:245 (Feb. 23) 1939.

Two cases are reported of dementia paralytica in girls 14 years of age whose mothers had positive Wassermann reactions. The symptoms began when the children were about 10 years of age, with backwardness in school and "nervousness." Examination some years later displayed dementia, abnormal pupillary reflexes and positive Wassermann reactions in the blood and in the spinal fluid. The cell count of the spinal fluid was respectively 20 and 42 per cubic millimeter. Both girls were given malaria and antisyphilitic treatment, without success. The author emphasizes the importance of early diagnosis and early treatment.

WALLGREN, Göteborg, Sweden. [AM. J. DIS. CHILD.]

Society Transactions

METROPOLITAN DERMATOLOGICAL SOCIETY

THOMAS N. GRAHAM, M.D., *President*

ANTHONY C. CIPOLLARO, M.D., *Secretary*

New York, May 19, 1941

A Case for Diagnosis (Avitaminosis with Lesions of Erythema Multiforme). Presented by DR. RICHARD J. KELLY.

A white man, first seen by me on May 15, 1941, complains of an eruption on the dorsa of the hands, around the neck above the collar line and on the trunk and extremities. This eruption has been present intermittently for more than a year. The eruption on the hands and neck appeared first and has been characterized by beefy redness, crusting and scaling. The lesions on the trunk, arms and thighs consist of annular plaques with raised erythematous borders and clear centers. He states that he has been on various diets during the past year and that he has taken no medications or alcohol.

DISCUSSION

DR. HENRY D. NILES: I think the two diagnoses to be considered are some form of lymphoblastoma and eczema. I suggest making a histologic examination and a blood count in order to make a definite diagnosis.

DR. RICHARD J. KELLY: The lesions of erythema multiforme were not obvious today. The patient has been on a very unbalanced diet. The striking feature is that when the eruption began it was limited to the exposed areas. He has always worked outdoors.

Psoriasis Arthropathica. Presented by DR. ROYAL M. MONTGOMERY.

L. P., a woman aged 27, has had psoriasis for the past fifteen years. The nails have been affected for the past seven years, and she has had arthritic symptoms for five years. At present there are small and large scaly red patches throughout the scalp. The nails of all the toes are dystrophic, yellow and undermined with subungual scaling. Pains in the toes started five years ago. The big toes were swollen, and several small toes were also affected. There was some scaling between the toes, especially in the first interspaces.

Examinations of the toes and toe nails showed no evidence of tinea. Roentgenograms of the feet showed arthritic changes on the heads of the left third and fourth metatarsal bones, especially on the fourth. There were irregular areas of callus formation about the fourth metatarsal-phalangeal joint, with absorption of the periphery of the head. About the interphalangeal joint of the left big toe were inflammatory changes with destruction and proliferation of bone.

DISCUSSION

DR. RICHARD J. KELLY: I recently saw a man who was much more crippled than this patient. I gave him high vitamin B therapy with unconcentrated liver extract, and his arthritis cleared in four weeks. His psoriasis showed no change. He is being given vitamins A and D at present for the psoriasis.

DR. THOMAS N. GRAHAM: My impression of psoriasis arthropathica from the cases I have observed is that this form of psoriasis is particularly resistant to therapy. The course of the eruption is directly related to the arthritic changes, and

exacerbation of the arthritis is usually accompaned by a flare-up of the psoriatic lesions, regardless of what dermatologic therapy is being employed. Psoriatic involvement of the nails, I have found, frequently responds to roentgen ray therapy when other therapeutic measures have been ineffective.

DR. LAIRD S. VAN DYCK: Vitamin D in large doses, up to 300,000 U. S. P. units per day, might be helpful in this case.

DR. MAURICE J. COSTELLO: It is better to use only one thing at a time, to better determine what effects the cure. I have been successful in treating psoriasis of the nails with roentgen rays. The result is the same whether filtered or unfiltered rays are employed.

DR. HENRY D. NILES: I suggest the Goeckerman treatment for this patient. I have encountered 2 or 3 cases of psoriasis of the nails and arthritis in which the conditions have cleared up with this form of therapy. It gives more rapid results than other treatment. The lesions usually disappear completely in two to three weeks. The patient should be hospitalized; an ointment consisting of 3 to 5 per cent coal tar in zinc oxide is applied to the entire body every night, and a suberythema dose of generalized ultraviolet radiation is given every morning while a thin film of the salve is still on the skin.

DR. ROYAL M. MONTGOMERY: I have not had good results with roentgen ray therapy in cases of psoriatic nails.

Juvenile Tabes Dorsalis with Bilateral Primary Atrophy of the Optic Nerve and Charcot Spine (?). Presented by DR. FRANKLIN H. GRAUER.

C. L., a white man aged 35, born in Norway, has been blind since 1917, when he was 11 years old. At that time he went to an ophthalmic hospital, where he was told that the Wassermann reactions of his blood and spinal fluid were negative. He took medicine by mouth for two and one-half months. He then consulted a nerve specialist who told him he had "poor blood." He was given mercury salve and nine injections in the hip. Notwithstanding this treatment, he became totally blind within the year. Since 1920, when he was 14 years of age, he has been having lightning pains in the legs and shoulders and occasional pain in the abdomen. He received no further treatment until 1933, when, at the age of 27, he consulted a physician in another city because of difficulty in walking and received one hundred and two injections of tryparsamide. The Wassermann reaction of the blood and of the spinal fluid was positive in 1933. The Wassermann reaction of the mother's blood and of her spinal fluid was negative in 1934. In 1937 the patient had two flocculation and complement fixation tests, the reactions to which were positive. Examination of the cerebrospinal fluid revealed the following observations: partial fixation in 0.4 cc. of fluid and complete fixation in dilutions ranging from 0.6 to 1 cc.; cells, 1 per cubic millimeter; globulin (1 plus); protein, 37 mg. per hundred cubic centimeters, and a mastic curve of 2100000000. Because of intractable lightning pains he was given malaria therapy in 1937 and had a rather uneventful course of ten chills. Since then he has received sporadic treatment consisting of injections of bismuth and tryparsamide. Injections of tryparsamide were not considered contraindicated at this time because the patient was already totally blind, not even having any light perception in either eye.

Physical examination revealed the following significant facts: A healthy-looking man of 35 years was totally blind and had an abnormal gait. There was weakness of the right internal rectus muscle; the pupils were fixed to light; gross nystagmus was present; the disks were chalky white and sharply outlined; hearing was bilaterally diminished, with involvement of the eighth nerves; tendon jerks were all absent; there were no cremasteric reflexes; there was loss of light touch and vibratory sense below the fourth rib and of deep pain sense in the lower extremities; there were lumbar scoliosis and a hard bulging mass in the left

lumbar region; the urine was normal. A roentgenogram of the lumbar portion of the spine showed deformity of the lumbar vertebra, fragmentation and eburnation.

Roentgen examination in 1941 disclosed a scoliosis to the left in the lumbar region with rotation of the vertebrae. The vertebrae showed increased density, as well as deformity, and the intervertebral spaces have been almost eliminated from the level of the second dorsal to the fourth lumbar vertebra. The diagnosis rested between Charcot spine and hypertrophic osteoarthritis of the spine, with preference given to the former.

Since the malarial treatment the lightning pains have become definitely less frequent and less severe. The patient is presented for suggestions as to further therapy.

DISCUSSION

DR. MAURICE J. COSTELLO: The patient presents a fine example of syphilis of the central nervous system. I agree with the diagnosis of Charcot spine, because the patient does not have much limitation of motion of the spine in spite of extensive involvement of the vertebral column.

DR. LAIRD S. VAN DYCK: I agree with Dr. Costello.

Chronic Folliculitis and Furunculosis; Acne Varioliformis. Presented by DR. LAIRD S. VAN DYCK.

H. D. R., a man aged 41, an accountant, was first seen by me in 1935, with follicular papulopustules and furuncles on the face, scalp and chest and in the nuchal region. The eruption was of two years' duration. He had previously been treated by a dermatologist with roentgen rays, white lotion N. F., solution of sulfurated lime N. F. and chlorhydroxyquinoline (quinolor) ointment, with temporary improvement. After he received a few more roentgen treatments an infected sebaceous cyst developed on the right cheek, which continued to discharge pus for six weeks, until it was excised. The follicular pustules continued to appear in crops on the face and scalp in spite of treatments with an autogenous vaccine of Staphylococcus aureus, colloidal manganese, ultraviolet irradiation, ammoniated mercury ointment and a low carbohydrate diet. A trip to Florida was advised, and the patient stayed in the sun until he was tanned a deep brown, but the pustules continued to appear. Sulfathiazole (*2*-[paraaminobenzenesulfonamido]-thiazole) in doses of 60 grains (4 Gm.) a day for two days, with subsequent doses of 30 grains (*2* Gm.) a day for two weeks, resulted in complete clearing of the chest and scalp temporarily, but this treatment had to be discontinued when chills and fever developed. Injections of staphylococcus toxoid accompanied by the local use of staphylococcus bacteriophage in an ointment base have failed to stop the outbreaks. The Wassermann reaction of the blood was negative. Urinalysis, a blood count and chemical examination of the blood gave normal results. Cultures of pus showed Staph. aureus.

DISCUSSION

DR. HENRY D. NILES: The patient has had almost every form of therapy. I suggest a careful general examination, particularly in reference to diabetes and foci of infections. If a focus of infection is found and eliminated, this condition might improve. He should have a sugar tolerance test. If he has diabetes, that might account for the resistance to therapy.

DR. RICHARD J. KELLY: If the findings are still negative after Dr. Niles' suggestions have been followed, it might be interesting to test the patient with old tuberculin and to institute therapy with old tuberculin if necessary.

DR. THOMAS N. GRAHAM: Acne varioliformis sometimes responds to strong local applications. I recall a case in which roentgen ray and ultraviolet irradiation, as well as injections of staphylococcus vaccine and toxoid, was ineffective,

and the eruption was cleared with an ointment of 30 per cent sulfur precipitate in petrolatum. I agree with Dr. Niles that the patient should have a complete check-up for foci of infection.

DR. LAIRD S. VAN DYCK: He has had all the tests for the diagnosis of diabetes except the dextrose tolerance test. No focus of infection has been found in the teeth, tonsils or elsewhere. He has tried using a 15 per cent ammoniated mercury ointment, with no more benefit than was obtained from other salves.

Arthropathic Psoriasis. Presented by DR. THOMAS N. GRAHAM.

H. S., a white man aged 45, was first seen by me in the dermatologic clinic of New York Hospital on May 8, 1941. He presented an eruption of six months' duration, involving the hands, forearms and feet. The palms and soles presented hyperkeratosis with some fissuring and superimposed white scales. These areas were completely involved, there being no normal skin. The eruption extended to the sides of the hands and feet, in which locations there was not hyperkeratosis but erythema and scaling, which terminated in a fairly sharp border. On the dorsa of the hands were sharply marginated erythematous scaly patches. There were a few similar patches on the forearms.

The patient has severe rheumatoid arthritis which started one year ago. He has limitation of motion of the hands. All of his teeth have been removed. Since the onset of the arthritis he has lost 28 pounds (12.7 Kg.). There is no history of exposure to arsenic. The reaction to a Kline test of the blood was negative.

DISCUSSION

DR. HENRY D. NILES: It is interesting to encounter 2 cases of psoriasis arthropathica at one meeting, as this condition certainly is not common. Arthritis is the only internal condition frequently associated with psoriasis. I was interested to hear an arthritis specialist say that about one fourth of the patients he sees in an arthritis clinic have psoriasis. That ratio is not found in our cases of psoriasis, but occasional association with arthritis supports the theory that psoriasis is due to some metabolic disturbance. I recommend the Goeckerman treatment, as this treatment apparently helps the arthritis as well as the psoriasis. It sometimes helps the arthritis alone or the psoriasis alone and sometimes both. I gave this treatment at the New York Post-Graduate Medical School and Hospital to a patient who had arthritis but not much psoriasis. The arthritis improved in three weeks, but the psoriasis did not.

DR. ROYAL M. MONTGOMERY: An interesting feature in psoriasis arthropathica is that the arthritis is of the rheumatoid or infectious type and not of the hypertrophic type.

DR. MAURICE J. COSTELLO: Dr. Cecil once said that in 8 per cent of the many cases of arthritis observed by him there was psoriasis.

DR. THOMAS N. GRAHAM: The association of arthritis and psoriasis is probably observed more often by the arthritis specialist than by the dermatologist, since arthritis is usually a much more disturbing disease than psoriasis. An arthritis specialist of my acquaintance stated that he found psoriasis in about 10 per cent of his patients. A much smaller percentage, I am sure, of the dermatologist's patients with psoriasis complain of arthritis. Psoriasis arthropathica, however, is apparently a variant of psoriasis vulgaris and requires further tudy.

Argyria Due to Silver Arsphenamine. Presented by DR. MAURICE J. COSTELLO.

C. A., a woman aged 36, received sixty-three injections of arsphenamine intravenously and one hundred and twelve injections of bismuth subsalicylate and mercury salicylate intramuscularly. Fifty-four of the intravenous injections were of

silver arsphenamine. The dose of each is not known. After about the fiftieth injection she noticed a dusky blueness of her chin. This has increased since that time, and the discoloration now involves the face, the ears, the bulbar conjunctivas, the tongue and the hard palate.

DISCUSSION

DR. THOMAS N. GRAHAM: I agree with the diagnosis of argyria. The amount of silver arsphenamine which Stokes stated was safe from the standpoint of avoiding argyria is 8 Gm. If this woman had fifty-four injections she could not have had much more than the standard accepted dosage.

DR. MAURICE J. COSTELLO: Usually such definite bluish pigmentation is not seen deposited in the mucous membranes. When this condition developed the physician who was treating her stopped the arsphenamine therapy and gave her injections of bismuth subsalicylate.

Erythema Multiforme. Presented by DR. MAURICE J. COSTELLO.

J. R., a 20 month old boy, has had an eruption on his face and on the extensor surfaces of his lower extremities for months. The lesions consisted of primary thin-walled globular vesicles filled with a clear serous fluid; others were umbilicated and later became iris-like and multiform. Treatment thus far has consisted of application of a 5 per cent ammoniated mercury ointment, which has had no effect on the lesions.

DISCUSSION

DR. ROYAL M. MONTGOMERY: This case shows how erythema multiforme can simulate impetigo contagiosa.

DR. LAIRD S. VAN DYCK: I agree with the diagnosis.

DR. HENRY D. NILES: One still has to consider bullous impetigo. I should like to have a bacteriologic examination of the bullae. I suggest applying 20 per cent sulfathiazole in glycerin.

DR. RICHARD J. KELLY: There is no history of taking drugs. I agree with the presenter, but I also agree with Dr. Niles that impetigo should be ruled out.

DR. ANTHONY C. CIPOLLARO: I agree with the diagnosis of erythema multiforme.

DR. MAURICE J. COSTELLO: One thing against a diagnosis of impetigo is that there are 8 other children in the family and none of the others have contracted this disease. If one watches the evolution of the lesions one can see that the first is a tiny umbilicated vesicle which develops without erythema. There was not much improvement after application of a 10 per cent ammoniated mercury ointment.

Trichotillomania. Presented by DR. THOMAS N. GRAHAM.

C. S., a white woman aged 55, came to the dermatologic clinic of the New York Hospital complaining of loss of hair in the occipital region, which she first noticed eight months ago. Prior to that time she had been in the habit of putting her hair up in curlers and forming a tight knot in this region. Examination revealed an irregular area of the occipital region in which there were broken-off hair shafts. The scalp appeared normal, and there was no evidence of young hairs. The pharyngeal and corneal reflexes were normal. The reaction to a Kline test of the blood was negative. Microscopic examination showed no trichorrhexis nodosa.

DISCUSSION

DR. LAIRD S. VAN DYCK: I agree tentatively with the diagnosis, but I have some doubts as to whether this condition might not be caused by tension on the

hair by curlers. However, the patient uses curlers in front as well as in back, and there appears to be no loss of hair in the frontal or temporal regions.

DR. MAURICE J. COSTELLO: I think that if the hairs are rubbed off the condition should be called trichokyptomania.

DR. HENRY D. NILES: The feature which most impressed me was that, although the patient has fine straight hair, in this patch it is so coarse that it is almost negroid. It reminds me of the woolly hair nevus described by Sulzberger, in which there is a patch of negroid hair in a white person with straight hair.

DR. ROYAL M. MONTGOMERY: I do not agree with the diagnosis. My idea is like that of Dr. Niles. In the affected area the hair is curled up. In some areas the hair shafts are thicker than in other places. It is probably fractured at the thin points, as in monilethrix. I do not think the condition is monilethrix, however.

DR. RICHARD J. KELLY: I think the condition is trichokyptomania. I agree with Dr. Costello that the hair is broken off and not pulled out. There is an elevated area which suggests a nevus.

DR. ANTHONY C. CIPOLLARO: This condition is not a classic example of trichotillomania. The diagnosis of trichokyptomania should be considered.

DR. THOMAS N. GRAHAM: Miss Hopper examined many hairs. She did not find anything that would correspond to "twisted hair." The patient is extremely neurotic, and the history she gave is not reliable. She stated at one time that she pulled out the hairs and at another time that she thought the curlers were responsible for the condition. I think that it is impossible to decide whether the condition is trichotillomania or trichokyptomania. The distinction is not important.

Erythema Multiforme. Lichen Planus. Presented by DR. ANTHONY C. CIPOLLARO.

W. S., a man aged 45, a teacher of chemistry, was presented before the Manhattan Dermatologic Society on Jan. 10, 1939 (ARCH. DERMAT. & SYPH. **40**:294 [Aug.] 1939). He first consulted me on April 4, 1938 for an eruption which had been present since he was 10 years old. He has never been entirely free of lesions, although the condition has improved, especially during the winter months. He has been seen by many physicians, and the cause of the condition has been considered to be some focus of infection. During all of these years he has had all sorts of therapy, including vaccines, toxoids, sodium nitrite, roentgen rays, azosulfamide and sulfanilamide. This spring he had another exacerbation and became discouraged, as is easily understood; he went to the Mayo Clinic, where two biopsies were made; one showed dermatitis and the other typical lichen planus.

General physical examination showed no essential abnormalities. Examination for porphyrins made on several occasions also gave normal results. He shows sensitivity to ultraviolet rays of all wavelengths. Lesions even develop when the patient simply immerses his hands or elbows in warm water.

The patient presents lesions that are most prominent on the face, neck, hands and forearms. There are also lesions on the body. The lesions are violaceous or brownish red, round or oval, with many iris-like, and polymorphous. Some are simply dark red and others show infiltrated plaques.

The patient is presented for three reasons: (1) because of the duration of this eruption, namely thirty-five years; (2) because of the clinical picture of erythema multiforme and the sensitivity to both ultraviolet and infra-red rays, and (3) because of the histologic diagnosis of lichen planus, which does not seem to fit in with the clinical picture.

DISCUSSION

DR. MAURICE J. COSTELLO: I agree that this patient has lichen planus superimposed on erythema multiforme. I have observed him before, when he presented only erythema multiforme.

DR. HENRY D. NILES: I do not know whether one could make either diagnosis because the microscopic examination showed erythema multiforme at one time and lichen planus at another.

Pyoderma Gangraenosum. Presented by DR. ANTHONY C. CIPOLLARO.

J. S., a woman aged 38, was presented before the Manhattan Dermatologic Society on Nov. 12, 1940 (transactions not published) and before the Metropolitan Dermatological Society on Dec. 16, 1940 (ARCH. DERMAT. & SYPH. **44**:119 [July] 1941). The patient stated that she has had an eruption on her legs off and on for about five years. It is always worse during the winter months; during the summer months she has been free of the eruption with one exception, and that was during the summer of 1940. At the very inception the lesions appeared only on the right leg, but during the past few years they have been appearing on the left leg only.

The patient had pulmonary tuberculosis about ten years ago. She had no history of drug ingestion. She has been seen by many dermatologists and has had different forms of treatment, including treatment with tuberculin, roentgen rays, sulfanilamide and injections of liver.

The patient now presents scars on the right leg. On the left leg are two active lesions which show edema, erythema and an adherent slough. The fresh lesions always appear at the periphery of the old healed lesions. On the outer aspect of the right thigh within the past few days a small nut-sized nodular lesion has developed. It is not particularly tender. The lesion resembles that of erythema nodosum, but there is no fever. The patient stated that the ulcerated areas started as lesions similar to the one now present on the thigh.

The patient has been under my observation since Oct. 16, 1940. Of all the kinds of treatment I have used, the most effectual has been injections of liver and sulfathiazole, which she has taken intermittently since last October.

Several biopsies showed nothing but granulation tissue, and cultures have shown different organisms at different times, with the predominating organism being nonhemolytic streptococcus, Bacillus pyocyaneous, Staphylococcus aureus and intermediates of the Bacillus coli aerogenes group.

DISCUSSION

DR. MAURICE J. COSTELLO: I think the patient's condition has definitely improved since the last time she was presented. The new lesion on the right thigh rules out the diagnosis of dermatitis factitia. I think that this type of condition should improve with the administration of sulfathiazole. I believe that this patient has the chronic undermining type of ulcer described by Melaney caused by the microaerophilic streptococci

DR. LAIRD S. VAN DYCK: I agree with Dr. Costello.

DR. RICHARD J. KELLY: I recall this case because I was interested to see whether or not the lesions were factitial. The lesion on the thigh is definitely nodular. Below that there is an area of erythema. I do not think the patient would go so far as to give herself injections of anything in order to produce this effect.

DR. THOMAS N. GRAHAM: I agree with the diagnosis. I believe that ingestion of drugs can be ruled out as a causative agent.

DR. ANTHONY C. CIPOLLARO: I presented this patient again because I am convinced that she does not have erythema induratum of Bazin, as was previously suggested. I think that the cutaneous lesions are manifestations of lowered resistance to ordinary organisms. A biopsy showed only granulation tissue.

CLEVELAND DERMATOLOGICAL SOCIETY

H. N. Cole, M.D., *President*

C. G. LaRocco, M.D., *Secretary*

James R. Driver, M.D., *Reporter*

May 22, 1941

Bowen's Disease. Presented by Dr. Benjamin Levine and Dr. I. L. Schonberg.

E. C., a woman aged 53, in 1939 had a squamous cell epithelioma removed from the palate. She has been taking triple bromides for the past ten years.

Ten years ago a scaly and crusted lesion developed on the abdomen, which has persisted. Since then similar new areas have appeared on the trunk and on the thighs. From time to time crusts form on the affected areas, which on removal leave bleeding granular surfaces.

On the left side of the abdomen there is an erythematous polycyclic somewhat infiltrated lesion, the size of a half-dollar, covered with loosely adherent scales, removal of which leaves an oozing red papillomatous surface. On the left side of the trunk there are several pea-sized slightly elevated crusted lesions. There are similar lesions scattered over the right side of the abdomen, which are covered with yellow scaly crusts. In several of the areas there appears to be some superficial atrophy.

Histologic examination of a section of tissue taken from the large lesion on the abdomen showed the epidermis to be thickened and covered by a thick layer of cornified cells. This was due in great part to an increase in the number of cells of the prickle cell layer. The cells varied considerably in size and shape, and the nuclei were hyperchromatic. There were numerous mitotic figures present. The cytoplasm of the cells showed numerous vacuoles. For the most part the epithelium appeared limited by the basement membrane. In places, however, the basement membrane was poorly defined and the cells apparently extended down into the corium. The cutis just beneath the epithelium was infiltrated by many small round cells.

DISCUSSION

Dr. R. E. Barney: I offer a diagnosis of superficial multiple epitheliomatosis with possibly squamous cell degeneration. I do not believe the condition is Bowen's disease. A few years ago I had a patient with numerous lesions of this type on the body. One lesion showed clinical evidence that led me to suspect that it had undergone malignant change. It was excised and showed squamous cell epithelioma. I made five biopsies in all, and some showed squamous cell epithelioma while others showed basal cell epithelioma.

Dr. J. E. Fisher: Has the presenter considered the possibility of arsenic ingestion as a cause?

Dr. Benjamin Levine: The patient has taken bromides for ten years but no arsenic.

Dr. I. L. Schonberg: When the patient was first seen some of these lesions were greatly heaped up. I went into the history carefully to determine whether they might be due to bromides taken for a long time. I took specimens from other lesions for biopsy, and the observations were the same.

Dr. G. W. Binkley: In looking at the sections I was unable to discern changes of squamous cell epithelioma.

Moniliasis and Chronic Eczema. Presented by Dr. Benjamin Levine and Dr. I. L. Schonberg.

C. H., a man aged 72, was treated for a fungous infection of the feet in August 1935. A prostatectomy was performed in 1929.

When first seen, on April 28, 1939, he had an extensive eruption involving the crural and axillary regions and in folds of skin over the abdomen, consisting of a diffuse linear erythematous dermatitis with maceration. This eruption at times would improve under therapy, and then he would have relapses and his condition would become even more extensive than it was previously. At one time the eruption involved the greater part of the body. At times the maceration clears up, and at present it is considerably improved.

Cultures of scrapings from the affected skin revealed a yeastlike organism.

Histologic examination showed a small vesicle in the epidermis, and at one edge of the section in the epidermis there were two circular masses showing a central core of cornified cells in which there was a small refractile mass suggesting a retained hair. There was some slight vacuolation of the cytoplasm in the cells of the epidermis. There was slight edema of the underlying cutis with moderate pericapillary round cell infiltration. Two additional sections taken at various levels of the same block showed a similar picture. In a few focal areas there were small collections of polymorphonuclear leukocytes in the epidermis with greater vacuolation of the epidermal cells in these areas.

DISCUSSION

DR. J. A. GAMMEL: I think it should be possible by immunologic methods to show whether the organism found has any bearing on the patient's condition. I suggest that complement fixation, precipitation or agglutination tests be tried.

DR. I. L. SCHONBERG: This eruption has undergone a number of objective changes. When we first saw this patient, the various areas were covered by greasy scales, and at times the lesions looked like seborrheic dermatitis. We have tried various methods of treatment without much success. The cultures showed a yeastlike fungus, but, of course, one can find that in a great many cases of dermatitis of long standing. This may or may not be of significance.

Melanosis of Riehl. Presented by DR. CLAUDE B. NORRIS, Youngstown, Ohio.

M. C., a white woman aged 23, a housekeeper, had a persistent brown spot develop on her right forearm four years ago. Similar lesions developed on her forehead and at the right commissure of the mouth two months ago. The lesions began as red spots and later became brown. In the beginning itching was a prominent symptom, and this became worse during her menses. At present there are no subjective symptoms. She states that she does not take cathartics.

The lesions are a slaty, dark brown color. The larger one on the arm is 4.5 by 5 cm. and irregularly oval. Those on the face are 1 cm. or less in diameter. The borders of the lesions are clearly defined. They are flat and smooth and show no inflammatory reaction.

DISCUSSION

DR. E. W. NETHERTON: From the history of exacerbations with redness and itching from time to time, I suspect the possibility of a fixed drug eruption. In spite of the fact that there is no history of the ingestion of phenolphthalein, I suggest that she be given some to see if it produces an exacerbation.

DR. GERARD DEOREO: The possibility of confectioner's coloring matter (containing phenolphthalein) used in cake frostings and ice cream should be investigated.

DR. GEORGE H. CURTIS: I recommend trying all the drugs known to produce fixed eruptions. They could be given one at a time without danger of a serious reaction.

DR. J. R. DRIVER: Further investigation into the possibility of contact photosensitization may reveal the source of this patient's trouble. Toilet waters and perfumes contain oil of bergamot and other essential oils which result in this type of pigmentation in sensitized persons.

DR. CLAUDE B. NORRIS, Youngstown, Ohio: I presented this case as an instance of melanosis of Riehl because I could elicit no history of the ingestion of drugs. I also asked the patient about the use of cosmetics but could get no history indicating them as the cause.

Keratosis Pilaris. Keratosis Pilaris Rubra Atrophicans. Presented by DR. HUGO HECHT (by invitation) and DR. BENJAMIN LEVINE.

R. J., a Jewess aged 17, was born with this disease, which she inherited from her mother. The eruption is present on the knees, elbows and extensor surfaces of the arms, forearms and thighs and is especially evident on the face, where it is symmetrically distributed over the cheeks. Here the pilosebaceous openings are enlarged and the papules are not as elevated or as well developed as on other parts of the body. On the outer parts of the cheeks and in the parotid regions the skin is diffusely red, granular and covered by numerous fine scars that form a reddish anastomotic network. The pilosebaceous openings are open and gaping or are filled with keratotic plugs which can be plucked out and are made up of keratotic and parakeratotic material. In some of the pilosebaceous openings devitalized lanugo hairs can be seen; in others the cicatrization has destroyed these hairs.

DISCUSSION

DR. HUGO HECHT (by invitation): There are two kinds of keratosis pilaris; one is the simplex and the other is illustrated in the case presented. We have presented this case because little has been written about this disease in the American literature. In 1889 some cases of keratosis pilaris rubra atrophicans were published by Brocq (*Ann. de dermat et syph.* **10**:339, 1889). I think that this patient has this condition. It is interesting to study the family tree. Here five generations have had the disease. In this family the mother has this condition and also the oldest daughter. The second daughter does not have it, but it is starting to develop in the third child, now 11 years old. I published (*Arch. f. Dermat. u. Syph.* **160**:50, 1930) a family tree, covering six generations and comprising about 250 persons, showing the incidence of keratosis palmaris et plantaris hereditaria. It was interesting that the condition in this family could be traced back to 3 brothers; one of these had keratosis palmaris et plantaris hereditaria; another was insane, and the third had diabetes. The taint of these diseases ran through six generations, with some of the members escaping, particularly some of the family that are now living in the state of New York. Others of this family tree had the keratosis, the insanity or the diabetes, depending on which of the first three brothers was their ancestor.

Pustular Psoriasis. Presented by DR. I. L. SCHONBERG.

T. G., a white man aged 34, for the past eleven years has had a recurrent pustular and blistering eruption on both hands. He has received various types of local applications, including roentgenotherapy, copper iontophoresis, desensitization, liver extract and injections of vitamin B_1 without benefit. The eruption cleared up for several weeks after the use of sulfanilamide. His general health has always been good. In 1917 a splenectomy was performed after trauma. A similar pustular and vesicular eruption occasionally develops on the feet.

On both hands extending to the wrists there are numerous deep-seated vesicles and pustules, many of which group together to form infiltrated plaques. Many of the areas are infiltrated, lichenified and covered by heavy scales. On the border of the palms there are several patches which are infiltrated and fissured. The nails of both hands are dry, lusterless and ridged. The palms perspire freely.

Staphylococci and streptococci were occasionally found in cultures. No fungi have been found on repeated examinations and cultures.

Histologic examination showed in the epidermis hyperkeratosis, parakeratosis and acanthosis. No definite vesicles were seen. However, there were a few small

collections of moderately distorted polymorphonuclear leukocytes. In one area the collection resembled a small intraepithelial pustule. No similar leukocytic infiltration could be seen in the nonkeratinized epithelium. The parakeratotic portion was relatively wide. In some places the granular cell layer was somewhat prominent and in other places absent. The rete pegs were relatively thick and deep. In some areas, there was slight intercellular and intracellular edema. In one area there was a collection of round cells in the acanthotic epithelium. The papillae were slightly edematous. Here, and in the superficial portion of the corium, there was a moderate perivascular round cell infiltration. The corium showed a moderate degree of scarring.

DISCUSSION

DR. J. R. DRIVER: This man presents a typical picture of dermatophytosis of the feet with vesicular lesions and onychomycosis of the nails of both hands and feet. The eruption on the hands at present seems to be a dermatophytid.

DR. J. E. FISHER: I saw this patient a number of years ago. At that time he had typical lesions of ringworm in the interdigital spaces of the feet and hands. Under treatment it cleared up for about three years. I believe he has a recurrence of his former condition.

DR. J. A. GAMMEL: I also thought this condition was a fungous infection. However, repeated search so far has failed to reveal a fungus. Nevertheless, further studies by direct examination of diseased tissue and cultures should be made.

DR. GEORGE H. CURTIS: In my experience ids on the hands are confined to the palms and to the palmar surfaces of the fingers. I should like to have the opinion of any of the members concerning the occurrence of such eruptions on the dorsa of the hands.

DR. BENJAMIN LEVINE: It is my opinion that ids may occur on any part of the hands.

DR. I. L. SCHONBERG: I have seen this patient intermittently for the past four years. Cultures were made on four or five different occasions. The tops of vesicles were used for the cultures. The only organisms were staphylococci and at one time streptococci. I went into all possibilities of foci of infection. Vaccines and foreign proteins have been used, and nothing seems to have done any permanent good. I, too, believe this man has a tinea infection of his feet, but clinically the lesions on his hands resemble so-called pustular psoriasis. It was on the histologic evidence that this diagnosis was made.

C. G. LAROCCO, M.D., *President*

J. E. RAUSCHKOLB, M.D., *Secretary*

JAMES R. DRIVER, M.D., *Reporter*

Sept. 25, 1941

Anorectal Lymphogranuloma Venereum with Stricture and Acute Arthritis.

All the cases were presented by DR. E. B. HEISEL and DR. MAX E. KRAUSE from the Department of Dermatology and Syphilology of the Cleveland City Hospital.

E. R., a colored woman aged 38, complains of a painful, swollen left knee and draining "boils" in the region of the genitals of five months' duration. She also

gives a history of difficulty in defecation, relieved by a colostomy seven years ago, and of painful swollen knees for about one year.

Her left knee is warm, edematous, tender to pressure and painful on motion. The perineum is the site of several communicating sinuses, from which there exudes a copious sanguinopurulent discharge. The rectum will admit only the tip of a finger.

The hemogram showed a moderate normochromic anemia and a mild leukocytosis. The urine was normal. The Frei and Ito-Reenstierna intracutaneous tests elicited strongly positive reactions. An intracutaneous test with a 1:1,000 dilution of old tuberculin elicited a mildly positive reaction. Serologic tests of the blood for syphilis gave negative results. Roentgenograms of the left knee and chest showed no evidence of disease. An attempt was made to aspirate the left knee, but no fluid was obtained. Gram-stained smears of material from the cervix and from the discharging sinuses showed no organisms characteristic of the gonococcus.

Therapy consisted of a short course of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and two longer courses of sulfanilamide (paraaminobenzenesulfonamide) given orally. The sulfanilamide concentration in the blood varied from 6 to 10 mg. per hundred cubic centimeters. The dose of each drug was 4 Gm. daily. The purulent discharge has decreased and the left knee is less painful, but the total result has not been remarkable.

Anorectal Lymphogranuloma Venereum in a Man.

S. O., a Negro aged 23, complains of a thick bloody rectal discharge since the latter part of 1937. The stools are small and ribbon shaped. He admits the practice of sodomy since early in 1937.

Rectal examination reveals a relaxed anal sphincter and a granular indurated anal canal. Five centimeters from the anal orifice there is a firm annular constriction which will admit only the tip of the finger.

The reaction to the Frei intracutaneous test was strongly positive and to the Ito-Reenstierna intracutaneous test negative. Intracutaneous injection of a 1:10,000 dilution of old tuberculin gave no reaction. Serologic tests of the blood for syphilis gave negative results.

Histologic examination of a section of tissue from the rectal stricture revealed fibrosis, chronic inflammation and ulceration.

Therapy has consisted of 4 Gm. orally, daily, of sulfanilamide (paraaminobenzenesulfonamide) for thirty days. The sulfanilamide concentration in the blood has varied from 6 to 10 mg. per hundred cubic centimeters. There has been a noticeable diminution in the amount of the discharge but no discernible change in the stricture.

Granuloma Inguinale with Esthiomene and Anal Stricture; Asymptomatic Neurosyphilis.

G. F., a 45 year old Negress, complains of swelling and ulceration of the vulva and perianal region of two and one-half years' duration. During six months' hospitalization in 1939 a colostomy was performed for anal stricture and the lesions healed. The ulceration rapidly recurred in April 1941.

The patient presents an extensive edematous beefy red ulceration involving the entire vulva, perineum, anus and intergluteal fold. The labia majora and minora, the prepuce of the clitoris and the entire vestibule are greatly hypertrophied.

Voided urine specimens consistently showed a moderate degree of albuminuria, many pus cells and occasional red blood cells. The hemogram revealed a mild degree of secondary hypochromic anemia. The blood and cerebrospinal fluid showed positive serologic reactions for syphilis. Repeated intracutaneous Frei tests gave negative reactions during 1939, but the reactions became moderately positive during the present hospitalization. Ito-Reenstierna intracutaneous tests

gave negative reactions. Smears of tissue treated with Giemsa stain showed inclusion bodies interpreted to be Donovan bodies.

Histologic examination of a section from the edge of the ulceration showed mild hyperkeratosis and acanthosis at the edge of the ulceration. The cutis throughout the section showed a dense infiltrate consisting chiefly of plasma cells with some lymphocytes and polymorphonuclear leukocytes.

DISCUSSION OF CASES OF LYMPHOGRANULOMA VENEREUM AND GRANULOMA INGUINALE

DR. H. N. COLE: The first case is interesting from the standpoint of involvement of the left knee joint. Some years ago H. S. Reichle and W. H. Connor (Lymphogranuloma Inguinale: Report of a Case with Involvement of Retroperitoneal Lymph Nodes and Probable Involvement of the Hip Joint, Adrenals and Kidneys, with Autopsy, ARCH. DERMAT. & SYPH. **32:** 196-203 [Aug.] 1935) reported a case of typical lymphogranuloma venereum. In the course of the disease arthritis of the hip and constitutional disturbances developed. At autopsy, typical lesions of the disease were found in the entire lymphatic chain, extending from the inguinal region along the retroperitoneal nodes to the diaphragm. There were, in addition, granulomatous lesions of the kidney, hemorrhagic infarction of both adrenals and chronic arthritis of the hip joint. The disease had certainly invaded the lymphatic apparatus beyond the local nodes. The extralymphatic involvement of the hip joint was most unusual. Tuberculosis was ruled out not only because of an absence of acid-fast organisms but also because of the character of the inflammatory granulation tissue. Moreover, there were no characteristics of a pyogenic infection. Here again is a patient with acute lymphogranuloma venereum and arthritis of one knee which cannot be explained in any other fashion. I am inclined to put this condition in the same category as that in the case reported by Reichle and Connor.

The third patient, G. F., with the extensive esthiomene is interesting because of the fact that she is suffering from granuloma inguinale and, as far as has been ascertained, does not have lymphogranuloma venereum. In view of the findings in this case and in others that my associates and I have observed in the last few years, it seems to me that we shall have to change our ideas about esthiomene. It is simply a symptom. While it is seen most frequently with lymphogranuloma venereum, it may also occur with granuloma inguinale, and I could conceive of its possibly occurring with other chronic ulcerative conditions in this location, perhaps in cases of chancroidal infection or even of tuberculosis.

The patient S. O. presents an example of the anorectal syndrome of lymphogranuloma venereum in a man. This may be explained in the same manner as in other cases of this kind in the past on the fact that the patient probably had a primary infection in that localization.

Annular Macular Syphilid, the Tabetic Form of Dementia Paralytica and Syphilitic Aortitis.

J. M., a white man aged 50, complains of an asymptomatic eruption of many years' duration. He has the tabetic form of dementia paralytica, which has not been treated, and syphilitic aortitis. He gives a history of a penile lesion twenty-five years ago. There is no history of the ingestion of any drugs, including cathartics containing phenolphthalein.

He presents a bilateral asymmetric brownish erythematous eruption on the trunk and lower extremities. The eruption consists of well demarcated, non-indurated, variously shaped macular areas, varying in size from 3 to 25 cm. Most of the smaller lesions are round and more erythematous but not so deeply pigmented as the larger ones. The largest lesion covers the left flank. It is roughly renniform in shape, has an arcuate border, is brownish red and is covered with grayish transparent scales. Throughout this lesion there are small, round, smooth, depigmented areas.

The hemogram and urine were normal. Serologic tests of the blood and cerebrospinal fluid for syphilis gave positive reactions.

Histologic examination showed a mild degree of hyperkeratosis and atrophy of the epidermis. The rete pegs were almost absent. The cutis was the site of a moderate round cell infiltrate, consisting chiefly of lymphocytes.

Therapy consisted of eleven malarial paroxysms followed by six intramuscular injections, each consisting of 2 cc., of iodobismitol with saligenin. He also was given 2 Gm. of phenolphthalein orally on five successive days. There has been no change in the eruption at any time.

DISCUSSION

DR. G. W. BINKLEY: I have received the impression that some of the members associate the syphilis of the central nervous system in this case with the cutaneous lesions as cause and effect. This is not so. The term neurosyphilid was proposed by P. G. Unna for late cutaneous syphilis which in his experience simulated the neuroleprids. The late syphiloderm clinically and histologically (but not bacteriologically) had an analogue in some of the cutaneous lesions secondary to neural leprosy. Unna (The Histopathology of Diseases of the Skin, translated by N. Walker, New York, Macmillan & Co., 1896) defined neuroleprid as follows: "By neuroleprides I understand all those affections of the skin caused by the lepra organism which owe their development, not like the lepromata to the direct attacking of the cutis tissue, but indirectly to its growth in the cutaneous nerves." Reasoning by analogy, the basis of a cutaneous neurosyphilid was proposed to be a peripheral neuritis due to Spirochaeta pallida.

Disregarding the mechanism of the production of the cutaneous lesions for the present, nevertheless, I would place this condition in that same group of late cutaneous syphiloderms. It is an example of erythematous pigmented "neuro" syphilid, of the macular type. A less pigmented example was that in the case Dr. Frank McDonald presented before this society in October 1938 (Erythroderma of the Hands and Wrists in a Syphilitic Patient, ARCH. DERMAT. & SYPH. **39**: 1073 [June] 1939). In his case the spinal fluid was normal. The erythroderma and hyperkeratosis subsided completely on antisyphilitic therapy, leaving a permanent residuum of triangular areas of vitiligo, surrounded by hyperpigmentation on the flexor surfaces of the wrist. I predict that the lesions in this case will respond as promptly to chemotherapy.

DR. H. J. PARKHURST, Toledo, Ohio: I do not feel qualified to discuss the neurosyphilid of Unna, but the condition in this case impressed me as being parapsoriasis. The premycotic stage of granuloma fungoides should also be considered.

DR. C. L. CUMMER: As I understand the neurosyphilid of Unna, it does not necessarily imply that the patient has neurosyphilis. I have observed only 1 case of neurosyphilid. It was similar to this case, but the border of the lesion was elevated and definitely paler in the center. Biopsy of material from the patient presented today shows a definite round cell infiltration in the upper part of the corium, which is suggestive of syphilis.

DR. R. E. BARNEY: I agree with Dr. Parkhurst. The eruption is compatible with a diagnosis of parapsoriasis.

DR. H. N. COLE: This patient has been under observation for some time. The lesions are annular and arciform and macular, with a suggestion of late of scaling. The patient has an old syphilitic infection, and a diagnosis of the annular macular neurosyphilid of Unna is suggested. One might think of a drug eruption, particularly one due to phenolphthalein. He stated that he had not taken any of this drug, but nevertheless phenolphthalein was administered. It made no change in the eruption. Therapy for the syphilis has had little effect on the eruption, and, as I understand it, such is the case in the neurosyphilid. Histologically, the process does show a sleeve of cellular infiltrate just below the epidermis, which might be interpreted as suggestive of mycosis fungoides. Certainly the patient has no subjective symptoms of the latter disease.

Sarcoid of Boeck; Latent Syphilis.

S. G., a Negro aged 16, complains of nonpainful nontender swelling under and at the angles of both jaws of two and one-half months' duration. He gives a history of having sexual intercourse on four occasions four years ago but states that he never had a penile sore. There is no history of cough, hemoptysis, night sweats or loss of weight.

He presents in both parotid areas symmetric, firm, fixed lobulated masses, 4 by 4 cm. In the region of the submaxillary glands there are symmetric, firm, smooth, fixed ovoid masses, measuring 3 by 2 cm. There is a firm, movable, discrete, left epitrochlear lymph node, 1.5 by 1 cm. The skin is clear except for a cicatrix on the anterior surface of the skin of the left shoulder, caused by a human bite. The tonsils are cryptic, of moderate size and are not inflamed. Examination of the corneas by slit lamp microscopy revealed no present or past inflammatory changes. There are no stigmas of congenital syphilis. He has a daily afternoon rise in temperature, varying from 0.9 to 1.8 F.

Roentgenograms of the chest showed enlargement of the hilar lymph nodes with a streaked infiltration extending outward in a fan-shaped fashion into both pulmonary fields. Roentgenograms of the small bones of the hands and feet were normal. An intracutaneous test with a 1:100 dilution of old tuberculin elicited a negative reaction. The Frei and Ito-Reenstierna intracutaneous tests gave negative reactions. Examination of the blood showed: 14 Gm. of hemoglobin per hundred cubic centimeters; 4,920,000 erythrocytes and 8,400 leukocytes per cubic millimeter; a differential count of 50 per cent polymorphonuclear neutrophils, 44 per cent lymphocytes, 5 per cent eosinophils and 1 per cent basophils, and 4.3 mg. of albumin and 5.4 mg. of globulin per hundred cubic centimeters of serum, with an albumin-globulin ratio of 0.79. Serologic tests for syphilis elicited strongly positive reactions.

Histologic examination of a specimen from the left epitrochlear node showed round and oval granulomatous lesions which almost effaced the regular structure. These consisted chiefly of epithelioid and Langhans giant cells with a few small lymphocytes. Many of these areas showed central necrosis. A section from a tonsil showed one isolated collection of epithelioid cells and several Langhans giant cells. Acid-fast stains of both specimens revealed no tubercle bacilli.

DISCUSSION

DR. H. N. COLE: This patient should not be passed without some comment. He presents a remarkable example of Heerfordt's disease (uveoparotid fever). He has a typical symmetric parotitis, but he does not show the usual ocular involvement that goes with this syndrome. The pulmonary changes are characteristic of Schaumann's disease, showing the increased shadows of the hilar node and the fanlike shadows extending into the lungs on each side. He also has a complete anergy, such as is found in this condition. In line with Schaumann's statement that the tonsils always show the changes characteristic of the disease, a specimen was taken and the pathologist made a diagnosis of tuberculosis. It is true that there are more giant cells than one would expect to see with lymphogranulomatosis benigna, but when one considers the case altogether a consistent picture of Schaumann's disease is presented.

DR. J. R. DRIVER: On the basis of the histologic examination, the hospital pathologist made a diagnosis of hypertrophic tuberculosis. I suggest that the patient be tested with avian tuberculin. In view of the fact that he has syphilis, it would seem to me that he should be given antisyphilitic therapy to see what effect it would have on this disease.

NOTE.—In line with Dr. Driver's suggestion, the patient was given eleven semiweekly injections of iodobismitol with saligenin and four intravenous injections of mapharsen, without any change in the picture.

Pemphigus Vegetans.

L. S., a Jew aged 46, complains of a sore mouth and superficial ulcerations on his entire body of six months' duration. The eruption began as a "blister" on the lower lip shortly after the extraction of a tooth. The lesions start as vesicles and bullae, which become pustular, break down and leave a raw, oozing, foul ulceration. There have been no remissions.

The scalp, neck, lips, axillas, unbilical region, buttocks, genitalia, inguinocrural regions and inner aspects of the ankles and feet are the sites of sharply circumscribed, symmetric vegetative ulcerations, covered with a foul seropurulent discharge. At the periphery of these lesions there are many vesicles and pustules. The distal phalanges of the fingers, the finger nails and the nail beds show fungoid vegetations and paronychia. The mucosa of the mouth is extensively involved, presenting a denuded ulcerated surface.

The urine was normal. The hemogram showed a moderate degree of leukocytosis and a relatively absolute polymorphonuclear leukocytosis, with 14 per cent eosinophils. Serologic reactions for syphilis were negative. The sodium chloride content of the blood serum was 420 mg. per hundred cubic centimeters and of the whole blood 356 mg. The blood serum contained 3.4 mg. of albumin and 4.1 mg. of globulin per hundred cubic centimeters. The albumin-globulin ratio was 0.84.

Histologic examination of a section taken through the edge of an ulceration showed acanthosis, mild hyperkeratosis and intercellular edema of the epidermis. There also were one large and many small intraepidermal vesicles and a leukocytic infiltrate in the epidermis consisting chiefly of eosinophils. The elongated dermal papillae and the upper portion of the corium were edematous, congested and the site of a severe leukocytic infiltrate.

Local therapy has consisted of débridement, daily potassium permanganate baths and applications of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) to the ulcerations. He has received 3 cc. of vitamin B complex (Smaco) intramuscularly daily for seven days. In the past two days he has received 12 Gm. of sulfathiazole orally.

DISCUSSION

DR. H. A. HAYNES JR., Akron, Ohio: I think it would be interesting to determine the calcium and phosphorus levels in the blood with the idea that if the calcium content is low it may be elevated with calcium or viosterol therapy.

DR. R. E. BARNEY: I would be interested to know on what basis a diagnosis of pemphigus vegetans was made. Usually when lesions develop in the mouth in cases of pemphigus vegetans the prognosis is bad. Yet this patient has had the disease for six months.

DR. F. M. MCDONALD, Akron, Ohio: Because of published reports of success from the use of the sulfanilamide and its derivatives, Dr. Hal Elson Freeman and I treated 8 patients with pemphigus with sulfathiazole in 1937 and 1938. One-half of those patients died, and it was our feeling that the therapy was of no particular value.

DR H. N. COLE: In the genitocrural folds and under the scrotum there were some characteristic fungating lesions. It may have been that Dr. Barney did not see these.

DR. E. W. NETHERTON: I should like to ask the presenters if in the cases they have observed at the hospital there has been a high degree of eosinophilia.

DR. E. B. HEISEL: There were 14 per cent eosinophils present in this case. Eosinophilia is not a constant finding in all cases of pemphigus. I should like to add that this patient was at the Mayo Clinic, where viosterol in oil was administered, without any benefit.

DR. H. N. COLE: I should like to ask Dr. Netherton whether he lays great stress on the eosinophil count.

DR. E. W. NETHERTON: Recently I had a case in which the condition clinically favored a diagnosis of dermatitis herpetiformis. Later lesions developed

in the mouth which were compatible with a diagnosis of pemphigus. The eosinophil count was 40 per cent in smears from bullae fluid. Itching was intense. There was very little toxemia, but the patient died suddenly of a vascular collapse. When the eosinophil count is high in the fluid from the lesions, I believe a diagnosis of dermatitis herpetiformis is more likely.

NOTE.—About four weeks after presentation the patient died. The autopsy showed superficial ulcerative changes in the large intestine and esophagus. There were also cloudy swelling of the liver and kidney and bronchopneumonia, probably secondary to changes in the mucous membrane of the bronchial tubes.

Parapsoriasis (Pityriasis Lichenoides Chronica).

M. H., a white man aged 50, complains of an asymptomatic eruption of six years' duration.

There is a symmetric, generalized erythematosquamous eruption, most pronounced on the trunk and thighs. It consists largely of poorly delimited erythematous, oval macules, most of which are covered with a fine adherent scale. The lesions vary from 0.5 to 2 cm. in diameter.

The hemogram and urine were normal. Serologic tests for syphilis gave negative results.

Histologic examination of a lesion revealed a moderate degree of hyperkeratosis, parakeratosis and acanthosis. The stratum granulosum under areas of parakeratosis was almost absent. There was a mild intercellular and intracellular edema. A few follicular plugs were noted. The papillary projections of the dermis showed edema and dilation of the blood vessels. Throughout the dermis there was a rather dense round cell perivascular infiltrate, composed chiefly of small lymphocytes. In some places it extended into the epidermis.

DISCUSSION

There was general agreement as to the diagnosis.

DR. FRANK M. MCDONALD, Akron, Ohio: I suggest intensive vitamin A therapy.

A Case for Diagnosis (Amyloidosis Cutis? Lichen Planus Ocreaformis [Lieberthal]?).

P. B., a white man aged 53, complains of an itching eruption involving the lower extremities and abdomen of one and one-half years' duration.

There is a papular eruption on the lower extremities, most evident on the extensor surfaces of the legs and lateral surfaces of the thighs. There is also a small group of papules on the right lower quadrant of the abdomen. The primary lesion is a discrete, round, firm, somewhat umbilicated papule, varying from 1 to 3 mm. in diameter and from brown to violaceous red. The papules are capped by a thin gray scale. Over the tibias the lesions are closely packed in mosaic-like arrangement.

The hemogram and the urine were normal. The serologic test of the blood for syphilis gave negative results.

Three sections of the skin were taken from the involved areas at different times for histologic examination. All had similar features. They were characterized by focal areas in which there was a separation of the epidermis from the underlying inflamed dermis. The epidermis in these areas was atrophic and umbilicated and at the center was filled with a thick keratin plug. The dermis adjoining the vesicular space was infiltrated with small round cells and showed proliferation of fibroblasts. There were some areas of pale pink-stained tissue with few nuclei. These did not stain like amyloid, and with the Van Gieson connective tissue stain they remained uncolored. The epidermis in other areas showed hyperkeratosis, acanthosis and an intracellular edema. Many hair follicles were plugged with keratin. In the subpapillary layer of the dermis there were streaked and sharply outlined collections of small round cells.

DISCUSSION

DR. EUGENE ARDAY: I wish to offer the diagnosis of keratosis follicularis in place of those suggested. My contention is based on the fact that the eruption is chiefly follicular and on my examination of the microscopic section. The latter shows that the pathologic process is essentially epidermal. The mouths of the follicles are plugged with horny material as a result of hyperkeratosis. There is a disturbance in the normal sequence of cornification, i.e., dyskeratosis, as shown by irregularly staining large epidermal cells with a clear cytoplasm. In the lower layer of the rete there are areas of separation called lacunas, which occur characteristically in keratosis follicularis. The basement membrane is essentially undisturbed, and the round cell infiltration in the corium is chiefly perivascular and too sparse for lichen planus. The final clinical outcome, of course, will determine the correctness of my contention.

DR. J. E. FISHER: I favor a diagnosis of amyloidosis cutis.

DR. R. E. BARNEY: In the section I did not see the changes characteristic of lichen planus, but there was a lesion on the scrotum that to me was definitely lichen planus.

DR. H. J. PARKHURST, Toledo, Ohio: I believe the condition in this case is identical with that described by Lieberthal as lichen planus ocreaformis. Amyloid degeneration can occur in almost any chronic pruritic dermatosis.

DR. H. N. COLE: Stains made for amyloid gave negative results. The histologic picture is consistent with lichen planus. There was a pretty good sleeve of round cell infiltration under the epidermis, which seemed to me consistent with the disease that Lieberthal described as a form of lichen planus.

DR. E. W. NETHERTON: Several years ago I saw a man with almost the identical condition described by Lieberthal under the title lichen planus ocreaformis. Later Dr. Fisher also treated him, and finally Drs. Cole and Driver saw the patient and used elastoplast occlusive dressings, which resulted in almost complete disappearance of the eruption. In that particular case the lesions were flat, shiny, quite discrete and uniform in size. These are also characteristic of the condition in the patient presented today. In spite of the fact that amyloid was not demonstrated, I believe this case is one of amyloidosis cutis.

DR. M. J. GIBANS, Akron, Ohio: On the side of the leg there is a scratch mark that has seven or eight papules that are typical of lichen planus.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

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Sept. 19, 1941

Epitheliomas and Dermatitis Factitia. Presented by DR. WILLARD M. MEININGER.

Mrs. E. M., aged 79, was first seen in the dermatologic clinic of Stanford University Hospitals in 1935. She complained of an eruption of six years' duration on the back of her neck. Numerous deep excoriations were present in the nuchal region. Occlusive dressings were applied. Some new lesions appeared at the margins of the old ones, but all the lesions were healed two months later. She returned in January 1941 stating that the ulcers had recurred in 1939. In addition, a similar lesion had appeared on the hand four months previously. Ulcers were present on the neck and on the dorsal aspect of the right third finger extending

onto the web between the third and fourth digits. Both areas had definitely indurated borders.

Histologic examination revealed a basal cell epithelioma of the neck and a basosquamous cell epithelioma of the hand.

Fractional roentgen therapy totaling 5,400 r was given through 0.3 mm. of copper filter over an area 5 cm. in diameter on the neck. The lesion on the finger was excised and a Thiersch graft applied.

Complete healing has not been achieved on the neck; new ulcers appear from time to time. The hand has remained healed. There is no evidence of metastases. The scattered keratoses on her face and hands are being observed, and she applies a bland cream to them.

DISCUSSION

DR. MERLIN MAYNARD, San Jose, Calif.: I think that there is no doubt regarding the factitial part of the ulceration. She received the Coutard type of therapy for three or four days. A week elapsed without treatment because she had a sore throat, and then she was given further roentgen therapy. If roentgen treatment is given daily, there will not be as much trouble with sequelae as if there are intervals between the treatments. I should consider radiodermatitis as a factor in the failure of the lesion to heal.

DR. N. N. EPSTEIN: I should like to ask whether a biopsy has been made of the present ulcer.

DR. WILLARD M. MEININGER: A biopsy has not been made of the last ulcer. About two weeks ago the patient had lesions on the neck which became secondarily infected. I think that is why the lesion looks as it does now. Radiodermatitis was considered in the differential diagnosis, but it seems unlikely.

DR. N. N. EPSTEIN: I think that one should make sure that there is no epithelioma present now.

Pemphigus. Presented by DR. N. N. EPSTEIN.

Mrs. I. S., a white woman aged 43, was well until five months ago. At that time a dusky, erythematous, finely scaling and herpetiform dermatitis appeared on the nose. Successively, thin-walled small bullae appeared on the trunk, followed by a few on the scalp and extremities. Two months ago bullae appeared in the mouth.

Her general health has been good. Urinalysis, blood count and tests for phenolsulfonphthalein urinary excretion and blood nonprotein nitrogen gave normal results two months ago.

Treatment was started two months ago. Vitamin D, 300,000 U.S.P. units daily, was administered for a short period, with little benefit. She was hospitalized from July 7 to July 18, 1941. Dihydrotachysterol, 25 mg. daily, was given for one week; the dose was then increased to 37.5 mg. daily, and this was maintained for two weeks following her discharge from the hospital. Calcium gluconate, 12 Gm. daily, was administered orally during the same period. On this regimen few new lesions appeared, with involution of most of the old lesions. An estimation of the urinary calcium output during this period indicated that a progressively increasing amount was being excreted until a level definitely above normal was attained. For the past month the patient has taken decreasing amounts of vitamin D, from 500,000 to 200,000 U.S.P. units daily. For the past week she has discontinued taking all medication.

DISCUSSION

DR. H. E. MILLER: I think that it would be impossible to make a diagnosis of pemphigus on the present basis of the lesions, which are clearing.

DR. N. N. EPSTEIN: It is difficult to make a diagnosis of pemphigus from the patient's present condition. However, I feel that the diagnosis of pemphigus is probably correct because she has had bullae since March of this year. In

addition, she has had definite lesions in her mouth. The effect of therapy has not been dramatic. The lesions gradually decreased in number. Previously half a dozen lesions would develop in the course of a week. The combination of dihydrotachysterol with calcium gluconate, followed by vitamin D, seems to have been beneficial.

Arsenical Keratoses. Presented by DR. N. N. EPSTEIN.

R. J., a white man aged 58, came to the dermatologic clinic of Mount Zion Hospital on Aug. 15, 1941 because of keratotic lesions on his hands and feet. These first appeared thirty-four years ago. Solution of potassium arsenite U.S.P. in tablespoonful doses had been given for several weeks thirty-five years ago because of extensive psoriasis. The psoriasis had persisted, and ten years ago Finsen lamp radiation, roentgen rays and radium had been administered to the backs of the hands. Keratotic lesions on the backs of the hands have been treated with roentgen radiation and thorium X ointment.

At present there are discrete keratotic lesions on the palms, soles and dorsa of the hands. Between the thumb and the first finger of the right hand there is a keratotic fissured area which was secondarily infected when first seen. There is no evidence of psoriasis at this time.

DISCUSSION

DR. N. N. EPSTEIN: This patient has had a recurrent ulceration in the web between the thumb and index finger of the left hand for several months. There is evidence of previous irradiation in this area. The question arises as to whether or not the lesion should be excised. The lesions on the body are keratotic and are probably due to arsenic.

DR. H. V. ALLINGTON, Oakland, Calif.: One or two lesions on the back suggested psoriasis.

DR. H. E. MILLER: I am not certain whether the lesions on the backs of the patient's hands are due to psoriasis or to arsenic. He is a blond and of the age at which one would expect keratoses to develop without arsenic as a cause.

DR. MERLIN MAYNARD, San Jose, Calif.: This case was presented for suggestions as to therapy. I suggest freezing the lesions with carbon dioxide–acetone slush. I have treated such lesions by this method successfully.

A Case for Diagnosis (Ulcer of the Scalp). Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

I. N., a 73 year old white man, was seen on July 8, 1940 because of an ulcer on the occipital portion of his scalp. The lesion had been present for one year, during which time he had applied a number of local remedies without success. The patient presented a flat sharply marginated ulcer extending deeply. The border was erythematous. A pertinent history, a physical examination and twice repeated serologic tests of the blood failed to reveal any evidence of syphilis.

The lesion was removed with an actual cautery, and the site healed uneventfully. Histologic examination revealed only nonspecific inflammatory tissue. However, the ulceration recurred in March 1941 and failed to heal despite two further removals by cautery and six roentgen ray treatments, totaling 6,000 r. A biopsy in September 1941 was interpreted by Dr. G. Y. Rusk as showing nonspecific inflammatory tissue only.

In addition, the patient has used dressings of sulfanilamide in glycerin locally. He also received four injections of mapharsen and solution of potassium iodide N. F. by mouth without any beneficial effect.

DISCUSSION

DR. A. E. INGELS: This case is extremely interesting, but I do not think that the diagnosis can be made from a healed scar like this. Although repeated

Wassermann and Kahn tests have given negative reactions, it is possible that this lesion might be due to syphilis—it might be a gumma or one of the many other granulomas.

DR. H. V. ALLINGTON, Oakland, Calif.: Some wounds on the scalp, especially those following extensive and repeated destruction of tissue, heal slowly and poorly and break down easily. Whatever the origin of the ulceration may be, the present problem may be simply one of poor healing.

DR. H. E. MILLER: Am I correct in assuming that 6,000 r of roentgen rays was given to that area? I should hesitate to give as large a dose as this to a lesion of this type, particularly in view of the fact that histologic sections were reported to show chronic inflammation only.

DR. MERLIN MAYNARD, San Jose, Calif.: I think the only thing to do is to make an incision and remove the lesion entirely. It should be sutured rather than burned out. In this way one would obtain a good specimen for examination and a favorable scar.

DR. ERVIN EPSTEIN, Oakland, Calif.: When the patient was first seen, the lesion was superficial, so roentgen ray examination of the skull did not seem indicated. The lesion healed promptly the first time, and after being well for six months, it broke down. About roentgen ray treatment, of course in this case I did not have a diagnosis. The fact that the biopsies showed only inflammatory tissue would not prove that the lesion was not an epithelioma. It is hard to realize that the lesion does not look much different from the way it appeared when the patient was first examined.

NOTE.—Roentgenograms taken later revealed no involvement of the skull. An enlarged lymph node developed just below the ulcer three weeks after presentation. Histologic examination of this node showed metastatic carcinoma.

Chronic Migrating Pyoderma Associated with Psoriasis Simulating Specific Granuloma. Presented by DR. A. E. INGELS.

F. D. S., a white man 59 years of age, a salesman, presents a large tumor-like granuloma of the upper part of his right arm surrounded by and adjacent to red infiltrated areas, which are in the healing stage, representing the remains of similar tumors. Similar granulating masses, partly ulcerated, are seen on the ankles and thighs.

The patient has had intermittent psoriasis for the past twenty years. In May 1941 the psoriatic eruption became irritated and inflamed on the right arm, ankles and thighs. Gradually large tumor masses were formed in these areas. At this time the patient showed large fungating masses on the arm involving the anterior and medical aspects. The tumors were pierced by pointing abscesses. The largest tumor reached the size of half an egg or more. Other parts of the granulating masses were elevated 3 to 4 cm., forming flat areas of infiltrated pyogenic masses. Similar lesions showing more ulceration and less infiltration were present on his thighs and ankles.

A histologic section was prepared from one of the tumors and is presented tonight. The lesions did not respond to approximately three weeks of sulfathiazole therapy, so the patient entered Stanford University Hospital and received wet warm packs. Sulfathiazole therapy was resumed without any noticeable effect.

The lesion healed slowly, contrary to the behavior of an ordinary pyogenic granuloma. A further histologic study was made because of the possibility of a specific granuloma, but no substantiation for this suggestion was found.

When he left the hospital the lesions were improved 90 per cent.

Since then the lesions have become active again, the large tumor-like mass increasing in size presumably from lack of adequate care by the patient.

The patient has been given a reducing diet because of his extreme obesity and has lost 20 pounds (9.1 Kg.) or more.

Blood counts, urinalyses, serologic tests, tuberculin tests, coccidioidin tests, roentgenographic examination of the teeth and lungs, a blood bromide test and a dextrose tolerance test all gave normal results.

DISCUSSION

DR. A. E. INGELS: It is an obvious temptation to call such a condition mycosis fungoides. However, this case presents unusual features. In order to establish a diagnosis of mycosis fungoides there should be some resemblance to mycosis fungoides or to a lymphoblastoma microscopically. The blood picture is essentially normal. The patient has not had adequate treatment. The lesions have cleared spontaneously, regardless of the small amount of roentgen rays given him. This amount of radiation was insufficient to affect mycosis fungoides. The largest tumor practically disappeared; since then it has become active, which makes the diagnosis of pyoderma most tenable to me. Of course, one should remember that such conditions as mycosis fungoides may show nonspecific changes microscopically and later present a more definite picture.

DR. H. E. MILLER: I believe that this patient has a lymphoblastoma, probably mycosis fungoides. The histologic picture of this disease is not sufficiently characteristic in many instances to permit one to say definitely that a lesion is or is not due to this condition. There is usually a polymorphous infiltrate in the tumor stage, which may resemble a sarcoma or an infectious granuloma. Dr. Ingels states that the lesions have cleared with a small amount of roentgen therapy. This is one of the characteristics of the disease. Fractional treatments usually give excellent results, especially in the first few months of the disease. Radiation in doses used for the treatment of cancer, frequently given by roentgenologists, often causes such reactions as ulceration and general malaise.

DR. A. E. INGELS: I do not think that one can overlook the pathologic observations. Also, the patient showed definite exacerbation of the lesions as soon as he resumed his normal activity. As soon as he went to bed, they subsided. I think this suggests a pyogenic type of lesion.

Scleroderma. Presented by DR. CHARLES ALBERT SHUMATE for DR. HARRY E. ALLERSON.

R. P., a school girl aged 13, consulted us on April 8, 1941. She presented a serpiginous band of scleroderma on the dorsum of the left foot. The lesion measured 6 by 3 cm. and was of four months' duration. On the dorsum of the right foot was a small similar area of a few days' duration.

The patient's basal metabolic rate was found to be —26 per cent. Treatment with a pancreatic extract (padutin) and with thyroid was started, and a cod liver oil ointment was prescribed for local use.

There has been much improvement during the past two months.

DISCUSSION

DR. CHARLES ALBERT SHUMATE: About the same time that this girl came into the office, I saw another patient with scleroderma. This was a girl from St. Mary's Hospital, who was presented at the meeting of the San Francisco Dermatological Society on Feb. 7, 1941 (ARCH. DERMAT & SYPH. **44**:311 [Aug.] 1941). It was suggested by Dr. Templeton that she be given an insulin-free extract of pancreas. Her basal metabolic rate was + 8 per cent at that time, and it is — 4 per cent at present, so I have given her thyroid in increasing amounts, from ½ to 1 grain (0.03 to 0.06 Gm. daily). There has been no improvement in her condition since February 7. The case presented tonight is in marked contrast. There has been great improvement.

DR. MERLIN MAYNARD, San Jose, Calif.; I should recommend not large doses of vitamin D but rather long-continued therapy. Personally, I do not believe in massive doses of vitamin D, because such therapy is likely to be discontinued because of toxicity or high cost. Instead, I believe in moderate doses maintained for a long time. The majority of physicians giving vitamin D for pemphigus have not had good results because this therapy has to be maintained for a long time. Most clinicians expect the change to take place immediately.

DR. H. V. ALLINGTON, Oakland, Calif.: Do you think there is danger in giving 300,000 U. S. P. units of vitamin D over a period of a month?

DR. MERLIN MAYNARD, San Jose, Calif.: Yes, I think so. If a patient so treated were out of contact with the physician serious consequences might result. Hospitalization is necessary for patients given such doses; they should be watched carefully.

Psoriasis Arthropathica. Presented by DR. CHARLES ALBERT SHUMATE.

M. L., a housewife aged 55, was seen at St. Mary's Hospital in consultation with Dr. Horace A. Wald, of South San Francisco, Calif., on Sept. 8, 1941.

Examination showed generalized psoriatic patches and multiple painful swollen joints. She has had psoriasis for the past ten years and has been treated by various physicians, including several local dermatologists. Under their treatment the skin would at times be virtually clear. About eight months ago her fingers became swollen and painful, and for the past four months she has had pain in several of her joints.

Her general health has been good. However, since 1924 she has suffered from extreme depression and at times has attempted suicide.

The Wassermann reaction was negative. Examinations of the blood and urine showed no abnormalities. Roentgen ray examination by Dr. John O'Neill, of St. Mary's Hospital, of her right shoulder showed "a rongeured-out appearance of the outer end of the clavicle and of the acromion. The joint space was widened. The observations were those of a type of arthritis, closely akin to gout, which is occasionally seen in patients with psoriasis."

Therapy has consisted of 80 grains (5.2 Gm.) of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) daily, but this was discontinued because of anemia and leukopenia.

DISCUSSION

DR. ERVIN EPSTEIN, Oakland, Calif.: I agree with the diagnosis of psoriasis arthropathica. This case shows one of the most charactistic differences between arthropathic psoriasis and keratosis blennorrhagica. In keratosis blennorrhagica the arthritis is present before or appears simultaneously with the keratosis, whereas in psoriasis the joint involvement appears after the cutaneous lesions.

DR. G. V. KULCHAR: I thought this patient might be a good candidate for fever therapy.

DR. MERLIN MAYNARD, San Jose, Calif.: Has any one had any experience with gold therapy for this type of condition?

DR. N. N. EPSTEIN: I treated 1 patient with injections of a gold compound. There was no improvement in either the psoriasis or the arthritis.

A Case for Diagnosis (Leprosy?). Presented by DR. JOHN FANNING, Sacramento, Calif.

A. K., 13 years old, entered the Sacramento County Hospital July 2, 1941 because of a sore finger and burns on the hand resulting from the "therapeutic application" of boiling water. His left arm and forearm showed first, second and probably third degree burns. Anesthesia of the region of ulnar and median nerve distribution was noted. The ulnar nerve was not definitely palpable. On the dorsomedial aspect, just below the left elbow, was a scarred purplish area about the size of a dime.

The patient's brother, K. K., aged 10, was brought to the hospital six days later. About nine months before he had noted "clawing" of the left hand and areas of anesthesia on the forearm and hand. He stated that he had caught his fingers in a door some time ago. A school nurse had attempted to splint the fingers. Physical examination revealed dark pigmented spots on his abdomen. His left hand was moderately clawed and anesthetic. Paralysis of an ulnar nerve was present; on his left forearm were areas of anesthesia below the elbow. His left ulnar nerve was enlarged. His left leg was anesthetic below the knee.

Blood counts and urine were normal for both patients. Frequent nasal smears failed to show any acid-fast bacilli. Histologic examination of lymph nodes and nodules showed no evidence of leprosy.

The patients' mother is under treatment for nodular leprosy.

DISCUSSION

DR. G. V. KULCHAR: In the case of the younger patient, I thought of acrosclerosis. How extensive was the burn in the other case?

DR. JOHN FANNING, Sacramento, Calif.: About as extensive as you see from the scar. The burn healed rapidly.

DR. H. E. MILLER: I think that both children have a neural type of leprosy. I think it would be difficult to explain such lesions in 2 children of one family on any other basis. The facts that organisms have not been found and that the characteristic pathologic changes are not present do not rule out this diagnosis.

DR. H. V. ALLINGTON, Oakland, Calif.: Is the anesthesia of the left leg definite?

DR. JOHN FANNING, Sacramento, Calif.: Yes.

DR. A. E. INGELS: I thought that there was thickening of the ulnar nerve. One could feel nodular lesions on the ulnar nerve. The histologic picture is hard to evaluate. The sections are poor, but there is a suggestion of the granulomatous tissue seen in leprosy. I suggest that more sections be cut and studied.

DR. F. H. STIBBENS, Oakland, Calif.: Have any nasal smears been made after the administration of potassium iodide?

DR. JOHN FANNING, Sacramento, Calif.: I do not think so.

DR. F. H. STIBBENS, Oakland, Calif.: That will sometimes increase the organisms in the nasal smear.

A Case for Diagnosis (Foreign Body Reaction?). Presented by DR. H. V. ALLINGTON, Oakland, Calif., for DR. H. J. TEMPLETON, Oakland, Calif.

D. H., a white man aged 27, was first seen June 13, 1941. He stated that he has been a barber for the past six years. He said that for the past three or four years hairs clipped from his customers' heads had penetrated the skin of the interdigital webs of his hands. These provoked a persistent local reaction and had to be pulled out.

During the week prior to his first visit an acute inflammation developed in the interspaces between the second and third and the fourth and fifth fingers of his right hand. It was necessary to incise and drain small abscesses in these areas.

Aside from the acute attacks of inflammation, there were lesions consisting of localized areas of infiltration surrounding small central funnel-like openings from which short hairs protruded. A biopsy was made and Dr. Paul Michael's report is as follows:

The microscopic sections showed the wall to be composed of an outer layer of thin fibrous tissue. Most of the wall was composed of stratified squamous epithelium which had undergone degeneration. Differential stains showed this to be squamous epithelium with retention of intercellular bridges. Some of the inner lining cells had been still apparently living at the time of removal, as their staining properties approached that of viable epithelium. The contents consisted of disintegrated squamous epithelial cells, granules of fat lipoid and segments of hair. No definite hair roots were observed, however. The segments of hair were short and were cut tangentially, giving rather angular ends. There were no foreign body giant cells, macrophages or other indications of a foreign body reaction. The cyst appeared to be a simple inclusion type based on a hair follicle retention, and included hair, sabaceous material and disintegrated epithelium. There was no microscopic evidence on which a foreign body type of cyst could be diagnosed. The pathologic diagnosis was subepithelial inclusion cyst.

DISCUSSION

DR. A. E. INGELS: I am at a loss to explain the nodules. Were the black threads actually hairs? I did not have the opportunity to examine them microscopically.

DR. H. V. ALLINGTON, Oakland, Calif.: Yes. The patient insists that they are hairs from customers' heads and that they penetrate the skin while he is cutting their hair. He states that the hairs expressed from these lesions are of various colors and textures.

DR. A. E. INGELS: One of the proofs would be whether there are any hair papillae.

DR. H. V. ALLINGTON, Oakland, Calif.: The ones I saw appeared to have no papillae.

DR. N. N. EPSTEIN: I do not see why these lesions should be cysts if the hair enters the skin from the outside. There would probably be a foreign body type of reaction but not a cyst.

A Case for Diagnosis (Xanthoma). Presented by DR. CHARLES ALBERT SHUMATE.

J. A., a man aged 43, was presented at the meeting of the San Francisco Dermatological Society on April 18, 1941 (ARCH. DERMAT. & SYPH. **44**:1148 [Dec.] 1941). Dr. Graves suggested that further laboratory work be done. I should like to report that the patient's basal metabolic rate was —16 per cent and the cholesterol content of his blood was 287 mg. per hundred cubic centimeters. Thyroid therapy was advised, but the patient refused further treatment. A few new xanthomatous lesions appeared on the dorsa of his feet.

A Case for Diagnosis (Leprosy? Sarcoid?). Presented by DR. N. N. EPSTEIN.

K. T., a Chinese man aged 53, was presented before the San Francisco Dermatological Society on April 18, 1941 (ARCH. DERMAT. & SYPH. **44**:1142 [Dec.] 1941). The mass on the neck was found to be tuberculous. Those who thought the diagnosis was sarcoid were correct.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

LOUIS TULIPAN, M.D., *Chairman*

TIMOTHY J. RIORDAN, M.D., *Secretary*

Oct. 7, 1941

Epidermolysis Bullosa Congenita (Two Cases). Presented by DR. JOHN H. HARRIS.

CASE 1.—R. P., a white woman aged 35, has an eruption which has been present since she was 2 weeks old.

There are numerous flaccid bullae and crusted lesions on both arms from the wrists to the elbows, with many similar lesions on the chest and neck and others scattered over the lower extremities.

There is no history of this disease on either the maternal or the paternal side of her family.

CASE 2.—C. P., a girl aged 3 years, daughter of patient R. P. (case 1), was born with blisters on the hands and feet and around the mouth and has had the eruption continuously since then.

The child now presents numerous bullae distributed over both arms, forearms, hands, legs and soles. Wherever the skin folds there are multiple scattered lesions.

The blood count was within normal limits. The Wassermann reactions of the mother, father and child were negative.

DISCUSSION

DR. DAVID BLOOM: The condition in these cases is the simple type, in contrast to the dystrophic type, of epidermolysis bullosa. This leaves slight, if any, scarring and is usually not associated with changes of the mucous membranes or nails. It is directly inherited from one generation to another, for it is transmitted according to the dominant type of inheritance. That is why, in a case of the simple type, a parent is frequently found to be affected. The dystrophic type, which is also hereditary, is not transmitted directly from parents to children, for it follows the recessive mode of inheritance. One may therefore find several children affected but not the parents.

Tinea Circinata Suggesting Tertiary Syphilid. Presented by DR. EUGENE F. TRAUB.

C. G., a woman aged 62, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, with a generalized eruption of two years' duration.

The patient presents pea-sized, pigmented and erythematous lesions on the legs. On the inner aspects of the thighs in the crural area there is a well defined papulovesicular lesion. A large violaceous patch with multiple necrotic nodules is seen on the buttocks. On the upper extremities there are discrete, pea-sized, brownish pigmented macules.

The Wassermann and Kahn reactions of the blood were negative.

Direct examination of scales from the buttocks and crural region showed fungi.

Biopsy of a specimen from the buttock showed fairly normal epidermis, with a moderate amount of edema in the upper part of the corium and a slight lymphocytic infiltration about some of the blood vessels.

A specimen taken from the inner aspect of the thigh showed acanthosis with parakeratotic scale, especially thick at the follicular opening. There was a moderate amount of edema in the upper part of the corium. The blood vessels were dilated with swelling of the endothelial lining. In places the cellular infiltrate consisted of a connective tissue response, and in other places there was a lymphocytic exudate about the blood vessels. There was some exudate also in the midportion of the corium. There were new blood vessels.

Both sections showed a nonspecific dermatitis.

DISCUSSION

DR. GEORGE C. ANDREWS: The spreading, marginated, lichenified patches on the buttocks are not so unusual in cases of this type of tinea. The lesions on the legs interest me most, because they look like excoriations. Some of them have become infected and crusted, and I do not believe these isolated lesions would show tinea.

DR. LOUIS CHARGIN: There are three important points against the diagnosis of syphilis. In the first place, the eruption is bilateral and symmetric, which are rarely true of tertiary syphilitic eruptions. Secondly, the eruption is superficial; in syphilis of this type the tissues are invaded more deeply. Thirdly, it is almost a rule that a long-standing and extensive syphilitic eruption would show many healed areas with scars.

DR. HOWARD FOX: From the clinical standpoint, I do not think there is any resemblance to syphilis. The eruption consists of diffuse red inflammatory areas with sharply demarcated borders which do not show distinct nodules. The presence of numerous scratch marks practically rules out syphilis. The itching is rather intense for tinea circinata, but the diagnosis has been proved by microscopic examination.

DR. MAURICE J. COSTELLO: The unusual feature of this eruption is the duration of about a year and a half. I saw a patient in the dermatologic ward at Bellevue Hospital with a similar, although more extensive, eruption of eighteen years' duration. It cleared up in several weeks under treatment with 10 per cent chrysarobin ointment.

DR. LOUIS TULIPAN: I think the picture is one that was described years ago as eczema marginatum, in a fairly common location. It is interesting to see the arrangement and its resemblance to tertiary syphilitic lesions. It would be interesting to make a culture in this case.

DR. EUGENE F. TRAUB: Examination of the urine showed no sugar or albumin, but tests were not made for other constituents. The histologic picture was consistent with a diagnosis of fungous infection. The case was presented to demonstrate a few unusual features, namely, the exceptionally severe pruritus and the deep excoriations, which suggested a nodular ulcerative lesion—hence the idea that the condition might be mistaken for a tertiary syphilid, as, incidentally, it had been.

Lupus Erythematosus Following Exposure to the Sun in a Patient with Healed Tuberculous Nodes and Healed Pulmonary Tuberculosis. Presented by DR. EUGENE F. TRAUB.

R. C., a woman aged 37, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, with an eruption which was first noted six or seven months ago after exposure to the sun in Florida.

A tuberculous lymph node developed on the right side of the neck fourteen years ago, for which an operation was performed a year later. Eleven years ago pulmonary tuberculosis was diagnosed because of hemorrhage, and a resection of the phrenic nerve was performed the following year. The patient received pneumothorax treatment for one and a half years, and the condition has been considered arrested for the past nine years.

On the forehead, the lateral aspect of the nose and the left side of the neck and chest, anteriorly, there are discrete and coalescent, sharply defined, nail-sized to coin-sized lesions of violaceous erythema, moderately infiltrated, some of which assume an annular configuration. The centers of these lesions are somewhat depressed and present slight follicular dilatation. The margins show firmly adherent scales. On glass pressure the infiltration does not fade completely. Along the hair line there are macular scaling lesions, particularly above the ears.

The results of Wassermann and Kahn tests and of histologic examination have not as yet been reported.

DISCUSSION

DR. MAURICE J. COSTELLO: I think one rarely sees patients with pulmonary tuberculosis and coexisting cutaneous tuberculosis, but patients with a history and clinical course similar to those in this case are seen more frequently. The patient may suffer first from tuberculous adenitis, some years later from pulmonary tuberculosis and still later from lupus erythematosus of this type. I think this patient should be investigated with the possibility of a tuberculous causation. One would probably find a hypersensitivity to intradermal injection of tuberculin. Patients with long-standing lupus vulgaris may eventually have localized pulmonary tuberculosis with torpid activity and slow progression.

DR. SAMUEL M. PECK: This disease and especially this type of case has always interested me. Disregarding the history of tuberculosis, there is a typical history of exposure to sunlight as a precipitating cause for the condition. Recent investigations all indicate that lupus erythematosus is a generalized vascular disease due to some toxin. It has not been stressed enough that this toxin is apparently a light sensitizer. It has never been clear in my mind whether the violent sunburn is produced because the toxin is present or whether a specific light wave has to do with the actual formation of this substance. The European literature, especially articles by Dr. Romel of Lausanne, Switzerland, has stressed the role of tuberculosis in this condition. Dermatologists in this country certainly are not of

that opinion. If tuberculosis plays a role, it is paradoxic that sunlight should be a contributing factor in lupus erythematosus, since the ultraviolet radiation is so beneficial in tuberculosis. Therefore, this patient should be of particular interest to us, but I agree with Dr. Costello that the history of tuberculosis is coincidental.

DR. E. WILLIAM ABRAMOWITZ: Goeckerman (Lupus Erythematosus as a Systemic Disease, *J. A. M. A.* **80**:542 [Feb. 24] 1923) reported a small series of cases of lupus erythematosus in which tuberculous adenitis was a prominent feature. European dermatologists, in particular Kren (Zur Pathogenese des Lupus erythematodes, *Wien. klin. Wchnschr.* **48**:193, 1935), have expressed the opinion that tuberculosis is the etiologic cause of lupus erythematosus and even of the retinitis that has been described as associated with the disseminated type of lupus erythematosus. In this country the majority of dermatologists feel that tuberculosis is a minor factor, because lupus erythematosus associated with any definite active tuberculous process is seldom seen.

DR. RAY H. RULISON: I was rather interested in this case because of the history of exposure to sunlight promptly followed by this eruption. I studied 3 cases in which there were tuberculosis and lupus erythematosus, an acute attack of which followed exposure to sunlight. I wonder if there is a certain type of photosensitivity in patients with tuberculosis which would tend to develop this reaction.

DR. GEORGE C. ANDREWS: Rollier, of Switzerland, an authority on the treatment of tuberculosis by ultraviolet radiation, established the fact that tuberculosis makes some patients extremely photosensitive. In the treatment of pulmonary and other forms of tuberculosis by sunlight, he always begins with extremely small doses, because otherwise it makes the tuberculosis worse. In regard to the relation between lupus erythematosus and tuberculosis, the pendulum swings back and forth: One thing is believed one year, and the opposite the next year. Usually in such instances there is a little bit of truth on both sides, and one should not completely cast out tuberculosis as a possible cause in some cases. Tuberculosis in this patient may be the underlying cause.

DR. E. WILLIAM ABRAMOWITZ: It is well known that heliotherapy is of value in the treatment of localized surgical tuberculosis, but in pulmonary tuberculosis sun bathing may be harmful, as it may activate unsuspected foci. This does not mean necessarily that the skin of such patients is photosensitive.

DR. FRED WISE: There is another point of interest in connection with therapy in a case of this kind. A patient with a similar condition was treated with filtered roentgen rays for adenopathy of the cervical glands, and areas of lupus erythematosus developed in precisely the regions in which the roentgen rays had been applied. A cone was used, and there was a circular patch of lupus erythematosus one week after the exposure. I therefore believe that a patient with this condition should not be subjected to radiation therapy of the affected glands in the neck.

DR. LOUIS TULIPAN: Years ago I made a study of porphyrin in patients with lupus erythematosus and was not able to find any difference between the urine of these patients and that of normal persons. I therefore agree with Dr. Abramowitz.

DR. EUGENE F. TRAUB: This discussion has brought up the question of the relation of lupus erythematosus to tuberculosis. Here is a patient who has had active tuberculosis. Now a great many persons have tuberculosis, so the mere finding of that disease in a case of lupus erythematosus does not prove that a relation exists. One just continues to accept these hypotheses year after year. My own feeling is that there is probably no relation between the two diseases. I think lupus erythematosus is the result of a toxic condition or bacterial allergy. For years I have searched for a focus of infection. From cultures obtained in these cases vaccines have been developed which apparently have benefited certain patients. The question of excessive ultraviolet irradiation could be discussed indefinitely, but it certainly appears to be a precipitating factor in some cases.

Mosaic Warts. Presented by Dr. Andrew H. Montgomery and Dr. Royal M. Montgomery.

A. S., an Austrian woman aged 45, has had the present eruption for the past four years. The lesions appeared first on the plantar surface of the right foot and soon spread to the left foot.

Covering the entire anterior portion of the plantar surface of the left foot there is a large hyperkeratotic warty patch in which many capillary tips are visible. Individual warty elements are grouped in a closely coalesced mosaic pattern. Small satellite warts fringe the posterior border. Three small verrucous patches are on the heel, and there are small warts on the side of the big toe, in the fold under the fourth toe and in the fourth interdigital web. In the central portion of the large patch papillary fibers can be seen trailing backward to the surface.

On the plantar surface of the right heel there is an irregularly shaped keratinized warty patch, about 1½ inches (4 cm.) in diameter, with outlying smaller warty patches. Scattered under the metatarsal heads of this foot are many isolated small single and compound lesions. There are verrucous lesions on the tips of the great and second toes.

The only warty lesions on the hands are beneath the nails of the left thumb and index finger and on the side of the left thumb. The palms are free.

Coincidentally, but entirely unrelated to the mosaic warts, there are chronic itchy eczematous patches on the dorsal surfaces of the ankles. Also, mild eczematous patches are present on the left elbow and on the flexor surface of the left wrist, extending to the dorsum of the hand. There are varicosities on the knees and a scar of an old ulcer above the left malleolus. A small ulcer is present below the right lateral malleolus.

Treatment of the mosaic warts has been deferred pending this presentation. We hope to present this patient again in about two months completely cured without the use of roentgen therapy.

DISCUSSION

Dr. George C. Andrews: I may be wrong in my understanding that Dr. Montgomery says that roentgen ray therapy should not be used in the treatment of mosaic warts, but I have cured some of them by this method, and so I believe some of them at least are curable by it. The ones Dr. Barnes and I treated were given heavy divided dosage (750 r) weekly for three or four weeks.

Dr. Ray H. Rulison: My own experience with mosaic warts has been rather unfortunate, except in 1 case, in which the soles were entirely covered. I gave the patient a general anesthetic and curetted the area thoroughly, and the warts entirely disappeared. The man was an alcoholic addict, and I had great difficulty getting him under the anesthetic. Whether the operation or psychotherapy was the cause of his cure I do not know.

Dr. Andrew H. Montgomery: I think this is about the two hundredth case of this condition that we have observed, and so many cases of radiodermatitis have been encountered that therapeutists must be warned to keep away from this form of therapy. We have about twenty photographs of the ill effects resulting from trying to cure conditions of this kind by roentgen ray therapy. The usual patches are so large that one does not dare to administer irradiation. This one could not be excised. We have treated some very small patches with desiccation but have found that the best method is with a 60 per cent salicylic acid paste, which acts only on the horny layer and not on the connective tissue or capillaries, together with applications of monochloroacetic acid or silver nitrate. I am sorry we did not think of shaving one of those patches to show the warty cores coalesced in a mosaic pattern.

Dr. Eugene F. Traub: What has impressed me most about roentgen ray therapy—and I continue to use it for all kinds of warts, including mosaic warts—

is that the size of the dose has little to do with the final outcome. If the lesion is going to respond, it will do so with a fairly small dose, but if the wart does not respond quickly there is no use increasing the dose. Cases have been recorded in which there is an area of severe radiodermatitis, the only thing to survive in the field being the warts.

DR. GEORGE C. ANDREWS: In keratoderma climactericum the keratoderma is around the periphery of the foot. This woman has some horny thickening around one heel that made me think of that; she has had it for four years. I think she deserves some study along these lines; perhaps even an estrogenic substance might be tried, together with other therapy.

DR. SAMUEL M. PECK: I agree with Dr. Traub about the effect of roentgen rays in many cases, but that interpretation depends on the amount of roentgen radiation and method by which it is applied. In the treatment of a small verruca, about 0.3 cm. in diameter, a relatively greater amount of roentgen rays must be given than in the treatment of a larger area, in order to accomplish the same result. In the treatment of a lesion smaller than 0.3 cm., which is carefully protected with lead, really large amounts of radiation must be given. I have had few failures when two exposures of 1,000 r each were given, a week apart, as compared to only 500 r. This certainly eliminates the factor of suggestion. Animal experiments which my associates and I have conducted showed that when an area of 0.5 cm. or less was exposed to doses of as much as 2,000 to 3,000 r, it failed to show clinical or even histologic changes of any importance. It is true that some change might have been noted if such exposed areas had been examined at longer intervals, such as a year or longer. This led to the conclusion that small warts must be given at least 1,000 r at any one treatment, with a total of at least 2,000 r, to obtain any real roentgen ray effect.

DR. DAVID BLOOM: I should like to ask Dr. Andrews if he would feel justified in giving five weekly doses of 750 r each in this case.

DR. GEORGE C. ANDREWS: If I were treating this patient I should give the wart on each foot 750 r weekly for three weeks.

Leprosy, Lepromatous Variety. Presented by DR. JOHN H. HARRIS.

I. V., a Puerto Rican woman aged 27, who has lived in the United States for seven years, is presented from the Metropolitan Hospital with an eruption which she first noticed on her legs seven years ago. Five months ago this eruption began to involve her face.

The patient now presents numerous flesh-colored nodules on the nose, the cheeks and the rim of the ears. There are also a few scattered nodules on the arms. There is a brownish red discoloration on the lateral surfaces of the legs, and scattered throughout this pigmented area are numerous bluish papules and nodules.

A nodule was removed from the arm and another from the rim of the ear. Histologic examination of these showed that the epidermis was uninvolved and that the entire lesion was present in the papillary layer and the deeper portions of the cutis. The lesion consisted of broad tumor-like infiltrations by large pale epithelioid cells with pale vacuolated cytoplasm, somewhat resembling xanthoma cells. There was no granulomatous change, and inflammatory cells were conspicuously absent. Ziehl-Neelsen staining revealed enormous numbers of large acid-fast bacilli arranged in clumps and packets in the pale cells. Many of the sweat gland acini were surrounded by these pale cells.

Smears of material from the nose showed numerous acid-fast bacilli. The blood count was within normal limits. The Wassermann reaction of the blood was strongly positive on Jan. 21, 1941.

A roentgen ray examination of the chest showed several small fibrocalcified areas in the extreme apex of the right lung, with no recent infiltration or consolidation and no pleural effusion. The heart was normal.

The patient has living with her a son, aged 9 years, in normal health.

She is now receiving diphtheria toxoid, azosulfamide (disodium-4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate), 5 grains (0.32 Gm.) three times daily by mouth, and antisyphilitic therapy.

DISCUSSION

DR. HOWARD FOX: The nodules on the face and the swelling, pigmentation and wrinkling of the backs of the hands are characteristic of the lepromatous type of leprosy.

I should like to say a word about terminology in leprosy. The terms nodular and anesthetic, which were formerly used to describe the two main types of the disease, were discarded at the Leonard Wood Memorial Conference on Leprosy, in Manila, in 1931 (Wade, H. W.: A Proposed Revision of the Memorial Conference Classification of Leprosy, *Am. J. Trop. Med.* **17**:773 [Nov.] 1937). It was then agreed to use the terms cutaneous and neural, with grades 1, 2, 3 and 4, according to severity and with combinations of these numbers for the mixed type. At the First International Congress on Leprosy, in Cairo, in 1938 (The Classification of Leprosy: Report of the Subcommittee on Classification, *Internat. J. Leprosy* **6**:389, 1938), the term cutaneous was changed to lepromatous, signifying nodules in which bacilli are plentiful. I am now using these newer terms, lepromatous and neural, for publication in the ARCHIVES.

Syphilitic (Early) Ulceration Associated with Vincent's Infection and Osteomyelitis of the Toe. Lymphogranuloma Venereum. Presented by DR. GIRSCH D. ASTRACHAN.

F. W., an American Indian aged 22, was admitted to the Metropolitan Hospital on Sept. 16, 1941, with a history of having had a penile sore seven months previously. This sore healed in a week and a half. Two months later a bubo appeared in the left inguinal region, which soon ruptured and left a draining sinus. At about the same time a blister developed close to the nail of the big toe on the right foot. The blister gradually increased in size and broke; a sore developed, and a purulent discharge appeared. The patient was treated in the Meinhardt Clinic, where a diagnosis of early latent syphilis was made, and he received eight injections of a bismuth compound.

Examination on admission revealed a dollar-sized, well defined, deeply ulcerated area with an indurated border on the lateral aspect of the right toe involving the dorsum. The surface of the ulceration was partly granular and partly covered with a grayish thick crust. The discharge was purulent and had a foul odor. The entire toe was tender and somewhat swollen. In the left inguinal region there were several brownish, cordlike, circumscribed swellings of the skin, scars and a few fistulas discharging seropurulent fluid.

The Wassermann and Kahn reactions of the blood were 4 plus on two occasions. Examination of the spinal fluid showed no evidence of syphilis. Dark field examination showed Spirochaeta pallida. A smear of material taken from the ulcer showed fusiform bacilli and spirilla (Vincent).

The results of chemical examination of the blood (urea nitrogen, creatinine and sugar) were normal. There were 5,220,000 red blood cells and 11,000 white blood cells, with 45 per cent lymphocytes, 40 per cent polymorphonuclear neutrophils, 4 per cent stab forms, 3 per cent basophils, 3 per cent eosinophils and 5 per cent monocytes.

The reaction to a Frei test was negative on September 25 and positive on October 7. An intradermal test for Ducrey infection gave a negative reaction.

The urine was normal.

Roentgenograms of the lungs and left hip were normal. Roentgen ray examination of the toe showed osteomyelitis of the terminal phalanx (evidence of erosion).

The results of neurologic examination were normal.

DISCUSSION

DR. DAVID BLOOM: Although destruction of bone by the virus of lymphogranuloma venereum has been reported in the literature, it occurred only, as far as I know, as an extension of the process from the glandular focus of the original region. I believe that in this case the ulceration and the osseous involvement are due to syphilis.

DR. FRED WISE: The question in this case is whether the patient's lesion is due to lymphogranuloma venereum or to syphilis, and the probabilities are much more in favor of syphilis, although I do not recall having seen a similar lesion of syphilitic origin. Nevertheless, syphilitic paronychia which has been neglected or has become resistant to antisyphilitic therapy should come under consideration. The patient has a positive Frei reaction and is probably a victim of both diseases.

DR. MAURICE J. COSTELLO: I recall a young man who was admitted to Bellevue Hospital with a generalized secondary syphilitic eruption and syphilitic paronychia affecting both great toes. While he was in the dermatologic ward this condition extended to involve all the other toes. The syphilitic process even caused a syphilitic osteomyelitis of the distal phalanges, as was noted in this patient. It finally cleared up under treatment with the hypertherm. I believe that this type of treatment is indicated for a persistent secondary syphilitic manifestation which is so resistant to ordinary antisyphilitic chemotherapy.

DR. E. WILLIAM ABRAMOWITZ: The lesions on the toes are apt to be the result of some peripheral circulatory disturbance, which may explain why the condition has been resistant to treatment. I think Vincent's infection may be eliminated.

DR. GIRSCH D. ASTRACHAN: The patient's condition has improved greatly in the last three weeks. In my opinion the condition is probably malignant syphilis (early or precocious tertiary), and the destruction was probably accelerated by the presence of Vincent's infection. There is a possibility that the associated osteomyelitis may also be caused by the syphilitic infection. Also of interest are the paradoxic results of the Frei tests (one negative and the other positive) in a case in which there are definite signs of lymphogranuloma venereum.

Dermatitis Lichenoides Chronica Atrophicans (Csillag). Presented by DR. JOHN H. HARRIS.

F. H., a white man aged 46, presents an eruption on the neck, which has been present for one year.

In the center of the neck is a whitish band 4 by 1.5 cm. This band is infiltrated and contains many fine blackish plugs. There is a similar band on the side of the neck, 4 by 1 cm., made up of isolated papules which are coalescing.

The Wassermann reaction of the blood was recently negative. The blood count was within normal limits.

Histologic examination by Drs. Satenstein and Sachs confirmed the diagnosis. In the subepidermic zone the connective tissue was seen to be becoming partly homogeneous (degenerative) and partly forming a fine network (reticulometamorphosis). In the midportion of the cutis the vessel walls were edematous and in places the swollen endothelium almost occluded the lumen. There was a perivascular infiltration consisting predominantly of lymphocytes. Scattered throughout the middle of the cutis were small round cells and an occasional wandering connective tissue cell. In the deep part of the cutis the vessels were dilated.

The epidermis was regularly thin and flattened. At one edge a cavity was formed by the splitting of the epidermis, and some fibrin and degeneration of the prickles could be seen within the cavity.

In the cutis directly beneath the basal cell layer in the greater part of the section the elastic tissue fibrils were very scanty.

None of the findings is associated with any of the lichens. This condition is definitely a process in the cutis with the epidermis secondarily involved.

DISCUSSION

DR. DAVID BLOOM: The microscopic report mentioned a band of homogeneous connective tissue in the subpapillary region and edema in the deeper part of the corium. These are the features of lichen planus sclerosus et atrophicus (Hallopeau). I may state, therefore, that clinically and pathologically a diagnosis of lichen planus sclerosus et atrophicus is justified.

DR. LOUIS CHARGIN: It is my impression that such conditions as dermatitis lichenoides chronica atrophicans (Csillag), lichen planus sclerosus et atrophicus (Hallopeau) and lichen albus are one and the same disease, best named lichen sclerosus.

Gonococcic Abscess of the Prepuce, Later Resembling a Chancre (Chancre Blennorrhagique of Gougerot). Presented by DR. NATHAN SOBEL.

M. M., a white man aged 43, was referred to the Central Social Hygiene Clinic of the Department of Health on July 28, 1941 by Dr. J. Levine. He had a lesion on the ventral surface of the prepuce at its junction with the shaft of the penis.

Gonococcic abscess of the prepuce, later resembling a chancre (Aug. 4, 1941).

In 1931 the patient had gonorrhea which lasted six weeks. The Wassermann reaction of the blood at that time was negative. In 1936 he received injections of strychnine and arsenic over a period of four months for vitiligo. A Wassermann reaction of the blood at that time was negative and a second time was 2 plus. In 1937 it was 2 plus. The patient had measles, pertussis and mumps in childhood and malaria at the age of 12 years.

The patient admitted frequent sexual exposure. Five days after the last sexual contact he noticed, on July 18, a moderately painful "lump" on the prepuce. This rapidly enlarged to the size of an olive and was greatly inflamed. Wet dressings of saline solution were applied, and on July 26 the abscess ruptured and much pus was expelled. The Wassermann reaction of the blood was negative. There was no urethral discharge.

Examination on July 28 revealed a slightly indurated lesion, 2.5 cm. in diameter, on the skin of the ventral aspect of the prepuce at its junction with the shaft of the penis. It was sharply demarcated, forming a saucer-shaped ulceration with a somewhat elevated border. The base of the ulceration was granular and covered with a mucopurulent exudate. There was no undermining of the edges and no surrounding erythema. Pressure on the lesion revealed no retention of pus. Between the lesion and the most dependent portion of the prepuce there were five pinhead-sized superficial pustules.

Dark field examination for spirochetes was negative on July 28, 29 and 31. Smears were negative for Ducrey bacilli on July 28, 29 and 31; however, the Gram stain showed organisms resembling gonococci.

The reaction to an intradermal test with Ducrey vaccine was negative on July 31.

The reaction to a Frei test (with human antigen) was negative on September 12.

Endoscopic examination on August 4 showed the mucous membrane to be slightly reddened, with few scar areas, but otherwise normal.

Smears and cultures for gonococci of material from the urethra and of the prostatic fluid were negative. Slight mucoid discharge was noted. This showed a moderate number of polymorphonuclear cells and many organisms, none of which resembled gonococci.

A culture of material from the cutaneous lesion showed gonococci on August 6. Cultures of urethral and prostatic material showed no organisms.

On August 8 cultures of material from the lesion and from the small pustules showed gonococci, and so did smears of material from these areas.

The Wassermann reactions on September 12 and 22 were 2 plus.

On October 2 the reaction to a Kline diagnostic test was doubtful (±); to a Kline exclusion test, 2 plus; to a Mazzini test, 2 plus, and to a Wassermann test, doubtful (±). (These tests were performed by Dr. C. R. Rein.)

On August 10 the patient was given tablets of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), 0.5 Gm. four times a day for six days. The lesion of the skin healed completely. At present scars remain at the sites of the lesion and of the small pustules.

DISCUSSION

DR. EUGENE F. TRAUB: This case is rather unusual, and I do not recall having noted another of this kind presented before this society. The condition really should not be so rare. I recall last year seeing an ulcer on the dorsal surface of a physician's hand caused by a gonorrheal infection. Perhaps a good many cases like this are not reported or presented at meetings simply because the condition is not recognized.

DR. LOUIS CHARGIN: Ulcerations of this type on the genitals of females suffering from gonorrhea are not at all rare, although they are not usually as severe as in this case; but in the male they are not common. Dr. Sobel's patient did not have a concomitant gonorrhea; this is important in proving the diagnosis. The diagnosis would have to be accepted if gonococci could be demonstrated in a biopsy specimen from the affected site.

DR. NATHAN SOBEL: I was unable to obtain a specimen for biopsy. However, gonococci were obtained from the small unopened pustule by smear and culture methods. This would speak against contamination, although the possibility of a mixed infection cannot be excluded.

MINNESOTA DERMATOLOGICAL SOCIETY

HENRY E. MICHELSON, M.D., *President*

FRANCIS W. LYNCH, M.D., *Secretary*

Minneapolis, Oct. 14, 1941

Congenital Syphilis (Gummas). Presented by DR. H. E. MICHELSON, Minneapolis.

Miss L. R., a white woman aged 19, first noticed two years ago areas of bluish discoloration on the left leg. Some of this discoloration disappeared spontaneously. These areas were somewhat painful and were more noticeable after the patient

went swimming in cold water. Two weeks before admission to the University Hospitals, some of these bluish areas ulcerated. New ulcers formed at intervals before she was admitted to the hospital, on Oct. 3, 1941. She has been treated with hot packs and flaxseed poultices. She received some salve from her local doctor.

On the lateral and the posterior surfaces of the left leg are numerous punched-out ulcers with undermined borders. The base consists of pus-covered granulation tissue. The lesions are painful. There is no lymphadenopathy. On the left thigh is a depressed hard scar representing a healed ulcer.

Since her admission to the hospital the ulcers have been treated with 5 per cent sodium sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in cod liver oil ointment; this treatment has resulted in healing. Serologic reactions of the blood for syphilis were 4 plus throughout.

Histologic sections were compatible with the diagnosis.

DISCUSSION

DR. O. S. ORMSBY (by invitation), Chicago: The result of treatment in this patient is interesting. It is another example of the striking effect sulfathiazole exerts in a diversified group of infections. From the description of the lesions when treatment was instituted and a study of their present appearance the remarkable change becomes evident.

DR. H. E. MICHELSON, Minneapolis: I first thought that because of the circumstances the condition was a serpiginous pyoderma, and the remarkable thing is that the lesions responded so well to sulfathiazole.

Angiokeratoma of the Scrotum. Presented by DR. S. E. SWEITZER, Minneapolis.

C. H., a white man aged 49, first observed reddish warty lesions on the left side of his scrotum ten years ago. At that time there were only five to ten pinhead-sized lesions. In the past five years the lesions have gradually increased in size and number until the entire side of the scrotum is involved. The lesions bleed on slight manipulation. There was no history of trauma, with the exception of a bilateral hernioplasty twelve years ago. The family history was negative for similar lesions.

The left side of the scrotum is covered by innumerable red warty papules, varying in diameter from 1 to 5 mm.

The histologic picture was compatible with the diagnosis.

DISCUSSION

DR. O. S. ORMSBY (by invitation), Chicago: This patient presented an excellent example of angiokeratoma of the scrotum described by Fordyce and later emphasized by Sutton and others, which is not the true angiokeratoma of Mibelli. The latter type occurs on the extremities and is characterized by telangiectatic and wartlike lesions on the extremities, especially on the hands and feet, usually in young subjects and those with a chilblain circulation. In the scrotal conditions there are simple telangiectatic or angiomatous lesions with or without hyperkeratosis.

DR. HAMILTON MONTGOMERY, Rochester: The microscopic picture was that of a simple angioma comparable to senile ectasia, the latter occurring as small discrete lesions elsewhere on the body. When these lesions occur on the scrotum, they tend to multiply and there may be some hyperplasia of the epidermis, but the newly formed blood vessels still retain their endothelial lining in contrast to true angiokeratomas, in which the epidermis itself may form part of the wall of a vascular space.

Lupus Erythematosus. Presented by Dr. S. E. Sweitzer, Minneapolis.

B. H., a white girl aged 12 years, first observed red areas on the cheeks early in July 1941 and subsequently similar areas on the back, forearms and fingers. The eruption was accompanied by itching and general elevation in the temperature to 101 F.

There were traces of albumin in the urine. She had been given 0.065 Gm. of bismuth subsalicylate intramuscularly every fifth day, sodium sulfathiazole 45 grains (3 Gm.) daily for one week and local applications.

There are crusted erythematous plaques which contain dilated plugged follicles on the cheeks, forehead, eyelids, back, dorsa of the fingers and arms. Examination of the blood showed hemoglobin 74 per cent (Sahli), white blood cells 3,670 and red blood cells 4,500,000, with neutrophils 46 per cent, lymphocytes 43 per cent, monocytes 5 per cent and eosinophils 6 per cent.

Histologic sections were compatible with the diagnosis.

DISCUSSION

Dr. P. A. O'Leary, Rochester: I have not been encouraged in the use of sulfanilamide and its compounds in the treatment of lupus erythematosus. In fact, it has been of no benefit whatsoever. However, I have been repeatedly impressed with the value of rest in bed in the treatment of the disseminated forms of lupus erythematosus, which as a therapeutic procedure appears to be the most valuable single suggestion there is to offer these patients. No doubt the avoidance of light is also of material value, but rest itself, I believe, is paramount.

Dr. F. W. Lynch, St. Paul: I certainly agree with Dr. O'Leary's statement of the importance of rest in the treatment of acute or subacute lupus erythematosus, but I think there are exceptional cases in which there is a favorable response to sulfanilamide therapy. I have in mind a recent example of prolonged remission after treatment with sulfanilamide in a case in which death was expected within two or three days of the time when I first saw the patient.

Dr. L. A. Brunsting, Rochester: For the most part, patients with lupus erythematosus who have been benefited by treatment with sulfanilamide and its derivatives have had the disseminated discoid type of the disease. I have seen no improvement under this form of treatment but, on the contrary, have noted an unusually high degree of reaction in patients with disseminated lupus erythematosus. Perhaps sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine), which is the least toxic of these drugs, should be given a more extended trial.

Dr. Hamilton Montgomery: In one third of the cases of acute disseminated lupus erythematosus that I have observed in the clinic the condition began as a chronic discoid type. In the majority of instances dissemination occurred independent of any treatment. All transitions between discoid and disseminate forms of lupus erythematosus can be seen histologically. In regard to the use of gold therapy in the acute and subacute types, there is a higher incidence of leukopenia the more acute the process is, so that in about 50 per cent of the cases of disseminate lupus erythematosus there is a moderate to severe degree of leukopenia. Leukopenia is a definite contraindication to the use of gold therapy.

Lichen Nitidus. Presented by Dr. H. E. Michelson, Minneapolis.

V. D. McF., a white man aged 27, an unemployed musician, first noticed lesions on his forearm two years ago after a Mantoux test. He did not believe that these lesions had changed in character or number since then. The patient is receiving collapse treatment for pulmonary tuberculosis.

On the flexor and ulnar surfaces of both forearms and on the glans and shaft of the penis are tiny shiny papules, some of which are umbilicated.

The histologic picture was compatible with the diagnosis.

DISCUSSION

DR. O. S. ORMSBY (by invitation), Chicago: Eighteen years ago Dr. Michelson made an extensive study and report on this disease and discussed its possible relation to tuberculosis. Since that time a number of papers have been written on the subject. Opinion at present is divided as to the relation. I should like to inquire whether Dr. Michelson has arrived at any more definite conclusions in this regard.

DR. H. E. MICHELSON, Minneapolis: I am of the opinion that lichen nitidus is not related to tuberculosis in any way. The only connecting link is the histologic picture, and even that does not strictly conform to a tuberculous granuloma.

Lupus Vulgaris. Presented by DR. H. E. MICHELSON, Minneapolis.

F. W., a white man aged 72, a retired railroad worker, first noticed a lesion on the right buttock fourteen years ago. The lesion has grown down on the thigh somewhat during the last few years. Reactions to serologic tests for syphilis have been negative. A roentgenogram of the chest in May 1941 was interpreted as showing "no definite evidence of tuberculosis."

He was given a course of twelve weekly injections of bismuth subsalicylate as a therapeutic test for syphilis, but there was no demonstrable change in the lesion.

On the right buttock is a lesion with an elevated, crusted, serpiginous border. The center consists of a smooth scar.

Histologic sections were compatible with the diagnosis.

DISCUSSION

DR. P. A. O'LEARY, Rochester: The Viennese concept that the onset of lupus vulgaris is always in childhood or in young adulthood has been repeatedly disproved in this country. Many patients I have seen have been in middle life or beyond when the lupus vulgaris first appeared.

DR. H. E. MICHELSON, Minneapolis: In the work at Glen Lake Sanitarium I have observed and have emphasized how late in life cutaneous tuberculosis may appear. In fact, I have noted more patients past 50 than children with colliquative tuberculosis. I have seen a large number of patients in whom lupus vulgaris began late in life.

Bowen's Disease and Keratosis. Presented by DR. S. E. SWEITZER, Minneapolis.

T. K., a white man aged 70, stated that six years ago he first noticed a small red plaque on the right side of the chest. There was no itching. The lesion became scaly and grew slowly. Two similar lesions appeared on the lower part of the back at the same time.

Examination shows irregular scaly plaques 4 by 3.5 cm. in diameter on the right side of the chest and two irregular reddish brown lesions in the sacral area.

The histologic picture was compatible with the diagnosis.

DISCUSSION

DR. O. S. ORMSBY (by invitation), Chicago: Bowen's precancerous dermatosis has been the topic of much investigation. I have had considerable clinical experience with the condition, and I think it presents a definite and characteristic clinical picture. The lesions are hyperkeratotic nodules having a serpiginous arrangement resembling the syphilodermas. Several different conditions have been classed with this disease on account of the histologic picture. Bowen's original description placed it among the precancerous conditions. It is now generally conceded to be a particular type of epithelioma. This patient presents

the clinical picture of superficial epitheliomatosis rather than Bowen's precancerous dermatosis. In the case of the patient discussed by Dr. Michelson there was one large patch on the shoulder. The clinical appearance of this condition was typical, with the threadlike margin and scaling center. In addition there was a nodule near the center of the plaque. The microscopic examination showed basal cell epithelioma in the margin, squamous cell epithelioma in the nodule and dyskeratosis in the scaly portion. The patient died of metastatic carcinoma. Concerning treatment in the present case, on account of the superficial character of the lesions, they should be eradicated without much difficulty.

Dr. H. E. Michelson, Minneapolis: Superficial epitheliomatosis is a good term, but it must be modified by the findings at biopsy, because they are not all of the benign type by any means; one may find all types and all combinations.

Keratosis Follicularis (Darier's Disease). Dr. S. E. Sweitzer, Minneapolis.

J. D., a white man aged 82, stated that his eruption was of thirty-three years' duration. It began on the face and gradually spread till it involved almost the entire body. He had many types of treatment, including 100,000 U. S. P. units of vitamin A daily by mouth. The latter was first given on Aug. 19, 1941, and since then he has shown decided improvement. In the patient's family history, his paternal grandfather, his father, brother, sister and two of his nephews had a similar condition.

Examination shows the scalp, face, sides of the neck, both axillas, sacral region, inguinal and pubic areas, palms and soles involved by the eruption. The lesions are round, yellow-brown, delled, keratotic papules. The nails of the fingers and toes are rough, dry and friable.

The histologic picture was compatible with the diagnosis.

Keratosis Follicularis (Darier's Disease). Presented by Dr. H. E. Michelson, Minneapolis.

N. A. L., a man aged 26, a bartender, first noticed a patch of dermatitis on the forehead in 1927. This lesion spread by peripheral extension over the rest of the face and down on the neck within the next year. The eruption caused no subjective symptoms, and there was no familial history of a similar disease.

The patient was first seen May 7, 1941, at which time a diagnosis of keratosis follicularis was made. He was treated until June 6, with 25,000 U. S. P. units of vitamin A. Since then he has received 240,000 U. S. P. units a day, with improvement.

The histologic picture was compatible with the diagnosis.

DISCUSSION OF CASES OF KERATOSIS FOLLICULARIS

Dr. L. A. Brunsting, Rochester: It is difficult to establish a direct relation between this disease and a deficiency of vitamin A, but some patients have been benefited by the proper treatment. The best method of estimating the degree of deficiency of vitamin A is the recording of thresholds of dark adaptation, procured by a reliable method. If treatment is to be carried out by the administration of large doses of this material, it should be given preferably by injection rather than by oral administration.

Mycosis Fungoides, D'Emblee Form. Presented by Dr. S. E. Sweitzer, Minneapolis.

Mrs. B. P., aged 54, after delivery thirty years ago, had a phlebitis of the left leg, which incapacitated her for about a year. Since then the left leg has been larger than the right and has always given her some pain. Ten years ago

masses developed in the left calf and disappeared after six weeks of rest in bed. Two and one-half years ago these masses recurred and persisted in spite of treatment. One and one-half years ago ulceration occurred in a pigmented area 1 cm. in diameter. This ulceration progressed in spite of all treatment until she entered the Minneapolis General Hospital the last of March 1940.

Examination then showed an ulcer covering most of the middle third of the left calf and extending three fourths of the way around it. The ulcer varied in depth from 0.5 to 5 cm. The border was precipitous and surrounded by an erythematous halo. The floor of the ulcer was covered by pink granulation tissue. Biopsy of the ulcer border and floor showed nonspecific chronic granulation tissue.

The ulcer failed to heal under all forms of therapy, and in September 1940 the leg had to be amputated below the knee because of toxic absorption. The patient made an uneventful recovery and was discharged from the hospital.

Two months later she again returned to the outpatient department and showed multiple painless subcutaneous nodules on the stump of the amputated leg on the right thigh, right popliteal fossa and over the right scapula. Several lesions subsequently became dusky red and ulcerated.

Serologic examination of the blood for syphilis gave negative results.

After the last meeting the diagnosis of the d'emblee form of mycosis fungoides was made. Roentgen ray treatments (600 r) through 1 mm. of aluminum were given to each lesion. The lesions disappeared following treatment. Small new lesions, 1 to 2 cm. in diameter, appeared two months ago in different areas.

The last blood count showed erythrocytes 4,500,000 and leukocytes 3,550 per cubic millimeter, with neutrophils 63.5 per cent, lymphocytes 19 per cent, monocytes 12 per cent and eosinophils 5 per cent. There was 84 per cent hemoglobin.

Histologic sections were not diagnostic.

DISCUSSION

DR. P. A. O'LEARY, Rochester: I do not agree with the diagnosis of mycosis fungoides, though I realize that histologic studies tend to support such a diagnosis. On the right calf and thigh are firm, linear and irregular plaques that in the absence of cutaneous involvement suggest a phlebitis of some type. The history of similar lesions of the left leg, with a persistent ulceration which eventually led to amputation, is to me more suggestive of a disease of the venous system rather than mycosis fungoides. The scattered scars would fit into a picture of vascular disease more readily than they would mycosis fungoides.

The knowledge of disease of the venous system is meager, owing to the tendency of the physician to base a diagnosis on what he feels with his finger tips rather than on information gained from biopsies or excisions of an indurated plaque. In the differential diagnosis in this case I considered phlebitis, periarteritis nodosa and panniculitis, but I believe that a dissection of one of the linear plaques from the calf will be necessary to make the diagnosis.

DR. HAMILTON MONTGOMERY, Rochester: The first section revealed most of the features of mycosis fungoides, including an infiltrate just beneath the epidermis. Other sections showed a decided degree of panniculitis of the subcutaneous tissue with apparently no immaturity in the white blood cells on casual examination. There was a denser infiltrate than one usually sees in nonsuppurative panniculitis. I saw no evidence of thrombosed vessels or other evidence to indicate periarteritis nodosa.

DR. E. A. STRAKOSCH (by invitation), Minneapolis: Sections from the excised nodule were shown to Dr. E. T. Bell and his staff, who agreed with the diagnosis of mycosis fungoides. Dr. O'Leary mentioned periarteritis nodosa, which was considered in the differential diagnosis, but I was unable to make this diagnosis from the histologic sections.

Parapsoriasis. Presented by Drs. H. G. Irvine and D. D. Turnacliff, Minneapolis.

A man aged 43 first noticed a few lesions on the flexor surface of the right arm three years ago. Since then new lesions have developed on the other arm, the body and the legs. He states that since the eruption appeared there has been no change in the size of the lesions and that none has disappeared. The eruption does not itch.

On the flexor surface of the upper part of each arm are round, fawn-colored lesions with dry adherent scales, from 1 to 2 cm. in diameter. On the body and on the upper parts of the thighs all of the lesions are symmetrically distributed and elongated in the lines of cleavage. Some of the older lesions are atrophic.

Since last January he has had 18 mg. of B_1 daily for three months and 10 mg. since then.

The lesions have all disappeared.

The histologic picture was compatible with the diagnosis.

Parapsoriasis. Presented by Dr. S. E. Sweitzer, Minneapolis.

A. K., a white woman aged 67, when she was 15 years old, first noticed during cold weather small red pruritic spots on her legs. At first these spots disappeared during the warm weather, but then they increased in size and number until they involved almost the entire body except the face. During the past few years the lesions have been present the year around, although they seemed to improve in warm weather. Subjective symptoms were limited at that time to some itching when the patient went out into the cold. There were no other members of the family suffering from a similar disease.

Examination shows that the legs, arms and back are involved by many large dull red patches with indefinite borders and covered with fine loosely adherent scales. Involved in like manner are the lower part of the abdomen and the breasts. On the lateral surfaces of the legs, especially the left leg, the eruption consists of shiny papules. The face is clear.

Several biopsies have been performed which showed a picture consistent with a diagnosis of parapsoriasis.

Parapsoriasis. Presented by Dr. H. E. Michelson, Minneapolis.

Mrs. G. H., aged 49, had three pimples on her chin eleven years ago. She treated them with iodine, and an erythematous weltlike eruption occurred, which spread over the face and then appeared in the groin. This eruption was treated with ointment and "a violet light." The swelling disappeared and the face cleared in about two weeks. After this, lesions were noticed on the body, which were pruritic at first and became scaly after the pruritus stopped. New patches have appeared at intervals since.

The hemoglobin was normal, and there were 10 per cent eosinophils. No abnormal or immature cells were seen. A lymph node removed for biopsy was described as a hyperplastic node. Serologic tests for syphilis gave negative results.

Except for a few small areas of normal skin, the entire trunk and thighs are involved by indurated scaly plaques. There are areas in which the skin appears atrophic and in which there is some telangiectasia. All areas have an irregular pigmentation.

The histologic picture was compatible with the diagnosis.

DISCUSSION OF CASES OF PARAPSORIASIS

Dr. O. S. Ormsby (by invitation), Chicago: Dr. Michelson's patient had infiltrated lesions together with pigmentation. If this condition is parapsoriasis it would be of the Brocq type. As a rule, the lesions of this disease are super-

ficial, the skin presents no infiltration, the area is brownish red with fine scales, there are no subjective sensations and the condition is resistant to all forms of treatment. In the present case an early stage of mycosis fungoides should be considered. I recall a similar case in which, however, there were telangiectatic areas in addition to lesions like those this patient presents. I have also seen what was apparently the Brocq type of parapsoriasis eventually develop into mycosis fungoides. In view of the long duration of the disease in the present case the last-named condition probably could be ruled out. The diagnosis to be considered is an atypical parapsoriasis.

DR. CARL W. LAYMON, Minneapolis: Several specimens for histologic examination were taken from Dr. Michelson's patient. Clinically, I am unable to decide whether the case is one of parapsoriasis or mycosis fungoides. After studying and discussing the microscopic picture, I believe that the most likely diagnosis is parapsoriasis.

DR. HAMILTON MONTGOMERY, Rochester: I believe the case presented by Dr. Michelson could be regarded as one of an atypical parapsoriasis. It is interesting that Dr. Lee McCarthy recently read a paper emphasizing that parapsoriasis does not merge with mycosis fungoides no matter what the form. Recent unpublished studies at the clinic would tend to support this concept and also the fact that the different forms of parapsoriasis remain as such and one form does not tend to merge with another. On the other hand, there were 5 or 6 cases in which the diagnosis of parapsoriasis was made clinically but in which histologic examination revealed features of mycosis fungoides; subsequently the condition proved to be the latter.

A Case for Diagnosis (Pyoderma? Pemphigus?). Presented by DR. H. E. MICHELSON, Minneapolis.

Mrs. A. S., a white housewife aged 59, first noticed a scaly lesion on the scalp in May 1940. Her local doctor treated it as ringworm. The lesion has spread with loss of hair in spite of treatment. In January 1941 the patient noticed a small vesicle on one cheek. Shortly thereafter a similar vesicle appeared on the opposite cheek. These vesicles ruptured, and the lesion on the cheek has spread by peripheral extension. The patient wears dentures.

The entire vertex is devoid of hair, and the area is oozing and covered with pus. There is a pustular lesion behind the left ear. On both cheeks are somewhat depressed erythematous lesions over which the skin shows a slight suggestion of cigaret paper quality. There are two areas which look as if they might be ruptured vesicles. On the palate are eroded areas which were vesicles.

Microscopic sections are not diagnostic.

DISCUSSION

DR. O. S. ORMSBY (by invitation), Chicago: It is not uncommon for pemphigus to begin in the scalp. I recall at least 2 or 3 instances in which what was supposed to be a pyoderma was present in the scalp for some time before typical lesions of pemphigus developed on other parts of the body. I feel that this diagnosis should be seriously considered for this patient.

DR. H. E. MICHELSON, Minneapolis: Last year in Chicago Dr. O'Leary brought up the point that he thought pemphigus was more benign in character in his last observations. The last 3 patients with pemphigus I have seen have succumbed rapidly, and in 1 of these the lesions began as a bullous dermatitis of the hands. I wonder if Dr. O'Leary's material has been running true to his observation.

DR. P. A. O'LEARY, Rochester: We have during the past few years seen two types of pemphigus vulgaris: One that runs a course of six or eight months and is

unresponsive to any treatment and a milder form with lesions of the skin and mucous membranes which are held in abeyance by sulfanilamide or one of its derivatives.

DR. CARL W. LAYMON, Minneapolis: In the past several months I have had an opportunity to treat about a half dozen patients with sulfathiazole, and in no case was the course of the disease materially changed.

A Case for Diagnosis (Lichen Planus?). Presented by DR. S. E. SWEITZER, Minneapolis.

S. K., a white man aged 84, first noted round pigmented lesions on both lower extremities many years ago. There was never any itching. He was hospitalized recently for treatment of gout.

There is an eruption on both lower extremities. The eruption consists of depressed brown angular lesions covered by a firmly attached grayish mottled scale. The lesions vary in size from 0.3 to 1 cm. in diameter, the largest being present on the calves, in which area the scales were more firmly attached and were still present. There seems to be no tendency toward confluence of the individual papules.

Beginning on Aug. 11, 1941, the patient received 300 mg. of ascorbic acid daily intravenously for sixty days without improvement.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester: The histologic section showed some lichenification and a rather dense infiltrate in the cutis with deposits of hemosiderin. Clinically there was little evidence of purpura; and the characteristics of the lesions were not those of purpuric lichenoid dermatitis of Gougerot and Blum, nor did the clinical picture fit in with Schamberg's disease. The histologic changes, however, would be consistent with either of these conditions. Angioma serpiginosum can be ruled out both clinically and histologically. I have not seen anything just like this.

Healed Scleroderma. Presented by DR. S. E. SWEITZER, Minneapolis.

S. B., a woman aged 52, was shown in December 1937 (ARCH. DERMAT. & SYPH. **37**:727 [April] 1938). At that time she showed a large area of involvement on the back, chest and abdomen and several smaller lesions on the left side of the neck and left thigh. All of the involved areas itched intensely, and the itching, the size of the lesions and the sensations of pressure steadily progressed until there was nearly a generalized involvement.

Many forms of treatment were tried without avail.

She is shown now four years later to demonstrate the outcome of this case.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: It should be noted that this patient originally had an extensive morphea rather than true diffuse scleroderma. Circumscribed scleroderma occasionally undergoes spontaneous involution, while the diffuse type does not.

A Case for Diagnosis (Erythema Induratum). Presented by DR. F. T. BECKER, Duluth.

Mrs. L. M. S., aged 38, first noticed an eruption on her right thigh in January 1941. It has given her no great pain or discomfort but has slightly increased in size. One lesion has developed on the right ankle and one on the right arm during the interim. This patient was hospitalized for pulmonary tuberculosis

from 1927 through 1929. A roentgenogram of the chest taken recently showed no activity of this condition.

There are several plaques, varying in diameter from 2 to 6 cm., on the right thigh, right arm and right leg. The skin over these is smooth and shiny. There is some induration. The color around the border is brownish red.

The histologic picture was compatible with the diagnosis.

DISCUSSION

DR. P. A. O'LEARY, Rochester: I favor the diagnosis of panniculitis of the nonsuppurative type rather than erythema induratum. This is the type of case in which I believe deep dissection rather than the superficial punch biopsy method is necessary for obtaining adequate specimens for histologic section.

DR. F. T. BECKER, Duluth: My first clinical impression of the condition in this case was localized scleroderma, especially because of the lesion on the lateral side of the right leg. However, the lesion on the upper part of the thigh and that on the arm are definitely nodular and subcutaneous. A specimen for biopsy was taken of this. Collagen and elastic tissue were normal. I could find no evidence of morphea. Unfortunately the specimen for biopsy was not deep enough to show the infiltrate, but there was a small lymphocytic infiltrate about the fat cells. It was my impression that the lesions were some sort of subcutaneous tuberculid because of the previous infection or possibly panniculitis.

BRONX DERMATOLOGICAL SOCIETY

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Oct. 23, 1941

A Case for Diagnosis (Necrobiosis Lipoidica Without Diabetes?). Presented by DR. LEO SPIEGEL.

A. L., aged 54, a housewife, born in Switzerland, has resided in this country for the past twenty-eight years. She was treated at the clinic of the Lenox Hill Hospital from April 17 to June 11, 1935. At that time she presented a lesion which was described as a yellowish infiltrated red patch containing numerous milia. The diagnosis was Bowen's disease. The patient received four treatments with filtered roentgen rays. She disappeared from the clinic and returned on May 15, 1941.

On the forehead there is a well defined yellowish plaque the size of a palm. It is smooth and slightly raised, with well demarcated borders. In the central part of the lesion a few confluent papules are present. A similar patch the size of a dime is on the left cheek. There are no subjective symptoms.

The Wassermann reaction was negative with both alcoholic and cholesterolized antigens. The reactions to Kline flocculation tests were also negative with both diagnostic and exclusion antigens. Examination of the urine showed no sugar or albumin.

Chemical examination of the blood showed 9.8 mg. of urea nitrogen, 0.5 mg. of creatinine, 3.3 mg. of uric acid, 98 mg. of dextrose and 69 mg. of diastase per hundred cubic centimeters. The carbon dioxide–combining power of the blood plasma was 58.6 volumes per cent (normal 53 to 77 volumes per cent). Examina-

tion of the blood serum showed 197 mg. of total cholesterol (52 mg. of free cholesterol and 145 mg. of cholesterol esters) per hundred cubic centimeters. The icterus index was 9.5.

Histologic examination by Dr. T. Riordan showed the following features: The epidermis was thinned; the rete pegs were obliterated, and the basal membrane was disorganized in places. The granular layer was beaded, and the edematous collagen was moderately infiltrated in the upper part of the corium with increased enlarged capillaries of the subpapillary flexus. A special feature of the epidermis in places where the infiltration was dense was vacuolation of the lower cells, suggesting vesicle formation or a subepidermal space.

Directly beneath the epidermis there was an amyloid-like area which was fairly regular in its width with occasional larger ovoid zones in which the material was faintly acidophilic with no cellular structure and surrounded by a delicate connective tissue capsule. Beneath these zones was a connective tissue stroma containing the usual appendages of the skin.

DISCUSSION

DR. SAMUEL M. PECK: I cannot offer a definite diagnosis. Three conditions occur to me: (1) local fat disturbance, perhaps in the nature of necrobiosis; (2) amyloid change of the skin, and (3) localized myxedema. I must admit that in the cases of local myxedema that I have observed the lesions do not resemble the one in this case. Amyloidosis can be ruled out or proved by the congo red test. Histologic examination did not suggest necrobiosis.

DR. PAUL GROSS: The histologic picture and the unusual clinical picture suggest lipoidosis telae elasticae (Kreibich).

DR. CHARLES LERNER: In considering the differential diagnosis, in addition to the suggestions made by Dr. Peck, the possibility of scleroderma should be mentioned.

DR. CHARLES WOLF: If the original diagnosis was Bowen's precancerous dermatosis, the lesion was probably scaly, erythematous and slightly infiltrated. Five years later there appears a xanthomatous-like lesion showing lipoid infiltration of the elastic tissue. I believe that in the evolution of pseudoxanthoma elasticum there is in the earliest stage an infiltrative process which is not clinically pathognomonic. In the course of time the elastic tissue disappears. I suggest the diagnosis of pseudoxanthoma elasticum.

DR. CHARLES A. GREENHOUSE: I believe that this case is one of lipoidosis cutis et mucosae, as reported in 2 sisters by Wise and Rein (ARCH. DERMAT. & SYPH. **37**:201 [Feb.] 1938). In their cases lesions of the mucous membrane were present, while in the case presented these were absent. However, without suitable staining of the material for fat and amyloid, it is impossible to draw definite conclusions.

DR. MAX JESSNER (by invitation): The color indicates a xanthomatous or pseudoxanthomatous lesion. I think that with the help of different stains it would be possible to determine the kind of degeneration that is present. Without a complete histologic study I am unable to make a diagnosis.

DR. WILBERT SACHS: It is not possible to corroborate the diagnosis from the section presented. Another specimen should be taken for biopsy and the tissue stained for fat and amyloid. Necrobiosis of any type cannot be identified in this section.

DR. LEO SPIEGEL: I realize that the histologic studies are incomplete and do not permit a definite diagnosis. Nevertheless, I believe that there is a lipoid disturbance of the skin not of the xanthoma type. There were no xanthoma or giant cells present on histologic examination.

A Case for Diagnosis (Erythema with Pigmentation). Presented by DR. LOUIS CHARGIN.

Miss A. J., aged 25, a clerk, has been suffering for the past three years with erythema of the face, associated with moderate pigmentation and occasional fine scaling. There are no subjective symptoms. The process has persisted in spite of a variety of therapeutic measures, including roentgen rays, lotions and ointments. Cosmetics as an etiologic factor have been excluded by patch tests. The patient states that she has not used bleaching agents.

The eruption is distributed over the anterior aspects of the cheeks and the chin. It is rather sharply outlined, so that the posterior half of the cheeks is entirely free of eruption.

Seborrheic dermatitis, the superficial type of lupus erythematous and contact dermatitis, as well as erythrose peribuccale pigmentaire (Brocq), have been considered as possible diagnoses.

DISCUSSION

DR. MARION B. SULZBERGER: Has the case been investigated for tuberculosis? I mention this because I have encountered many similar cases in which there were minute papules which in some places tended to coalesce, giving the cheek a yellow or brown appearance; these turned out to be so-called "micro" lupus miliaris faciei of M. Jessner. I suggest the following possible diagnoses: rosacea, lupus miliaris faciei and contact dermatitis. A biopsy would help establish the diagnosis.

DR. MAURICE UMANSKY: It would be of interest to know if the presenter observed changes in the intensity of the eruption on this girl's face on different days or at different hours of the day. In erythrose peribuccale this phenomenon is usually ascribed to the fact that the capillaries in the skin are dilated in a varying degree at different times. The presence of this variation would be in favor of the diagnosis of Brocq's erythrose peribuccale pigmentaire.

DR. LOUIS CHARGIN: There is a definite change in color at different times of the day. The patient is never free of the eruption.

DR. ARTHUR SAYER: The patient has an oily skin and a salmon-colored scaly eruption on the cheeks and forehead. These are definitely symptoms of seborrheic dermatitis. I do not believe that this diagnosis can be discarded merely because the patient did not respond to the antiseborrheic therapy, since it is known that seborrheic dermatitis is occasionally refractory to treatment. I believe that the condition will clear on a diet poor in fats and carbohydrates and with the local application of sulfur.

DR. LOUIS CHARGIN: I have not considered tuberculosis of any form and I do not now. There is slight erythema with some pigmentation showing a sharp line of dermarcation of both cheeks. Occasionally there is a slight amount of scaling. These features do not suggest any form of tuberculosis. I have naturally considered seborrheic dermatitis and do not hesitate to discard this diagnosis. The condition is possibly erythrose peribuccale but by no means a typical example. I cannot account for the margination.

A Case for Diagnosis (Poikiloderma Vasculare Atrophicans). Presented by DR. DAVID BLOOM.

V. De S., a youth aged 16, was previously presented before the Manhattan Dermatologic Society in October 1941 (ARCH. DERMAT. & SYPH. to be published). Since then there has been an increase in scaling on the chest, back and thighs. The areas of telangiectasia remained unchanged.

DISCUSSION

DR. CHARLES LERNER: Clinically, aside from the scaling, this condition is a typical example of poikiloderma vasculare atrophicans, but I cannot reconcile this diagnosis with the histologic picture. The section seems not to show any atrophy, although clinically it is unquestionably present.

DR. WILBERT SACHS: In the section there is no evidence of scaling. There is no suggestion of ichthyosis. There is telangiectasia present but no loss of elastic tissue. The clinical pseudoatrophy may be due to an infiltration with temporary disappearance of the elastica.

DR. SAMUEL M. PECK: It was my impression from a cursory examination of the section that there was definite atrophy. At the same time there was telangiectasia and diminution of the elastic tissue. Such histologic changes are certainly suggestive of poikiloderma vasculare atrophicans. It would be worth while to study this patient from the point of view of a vitamin A deficiency.

DR. LOUIS CHARGIN: I cannot offer a diagnosis. I do not think the case is one of poikiloderma. What the patient presents now resembles ichthyosis. Parapsoriasis must also be considered, but there is too much scaling present and the distribution is unusual.

DR. CHARLES A. GREENHOUSE: This patient was first seen at the clinic about five months ago, and it was agreed without hesitation that the condition was a typical example of poikiloderma vasculare atrophicans. The scaliness is not an unusual feature. It is also possible that this patient used an irritating ointment to intensify the desquamation.

DR. CHARLES WOLF: I believe this patient should be examined from the point of view of a vitamin deficiency. From questioning the patient and from the appearance of the eruption a vitamin A deficiency is likely.

DR. HENRY SILVER: The patient presents definite atrophy and telangiectasia characteristic for poikiloderma. It may be argued whether the poikiloderma is of the Jacobi type. There are, however, other forms of poikiloderma. One type, described by R. Mueller, shows poikiloderma-like changes as an end result by many dermatoses. Another type, described by Zinsser, is congenital or appears early in life and is probably a nevus-like condition with features of poikiloderma. The condition in the case presented seems to fit into this type.

DR. DAVID BLOOM: The diagnosis of poikiloderma was based on the presence of telangiectasia, atrophy and depigmentation. Although there were always some tiny adherent white scales present in the plaques, the scaling has definitely increased in the past few weeks, and one sees now diffuse scaly plaques on the lower part of the back. The suggestion of a possible vitamin A deficiency has been considered, and the patient will be examined from this point of view.

Papulonecrotic Tuberculid. Erythema Induratum (Bazin). Livedo Reticularis. Erythema Nodosum. Presented by DR. ARTHUR SAYER.

B. S., a white woman aged 34, married, born in the United States, came to Mount Sinai Hospital in 1934 stating that she had had active pulmonary tuberculosis in 1930 and 1931. She had a pulmonary hemorrhage in December 1930 and was sent to Liberty, N. Y., where she remained for about nine months. When she returned to the city in September 1931 her condition was considered arrested. Since then she has remained in New York, has felt well and has gained weight.

She had been seen at the hospital at frequent intervals. Fluoroscopic examinations of the lungs showed only fibrotic scars in the upper lobes of both lungs. Repeated examination of the sputum showed no tubercle bacilli. The patient continued to be in good health until May 1941, when there developed an inflammatory eruption on the legs. She was then referred to the clinic for treatment of the eruption.

On May 10, 1941 she presented on each leg about half a dozen erythematous nodules varying in diameter from 1 to 2 cm. They were moderately elevated and tender and extended into the subcutaneous tissue. There were also a few small erythematous papules scattered over the legs. A diagnosis of erythema nodosum was made. The smaller lesions were considered characteristic of papulonecrotic tuberculids.

At present the patient presents an ulcerated lesion on the right shin. The lesion is about 2 cm. in diameter, is not painful or tender and has been present for almost two months. Clinically the condition is erythema induratum (Bazin). There are also several scattered small dark red papules on the legs and forearms and a dozen or more whitish and violaceous, slightly depressed small scars. These lesions are papulonecrotic tuberculids. In addition, there is a marble-like apperance of the legs and lower parts of the thighs due to the reticular arrangements of the superficial veins. The patient states that this marble-like skin has been noticeable for several years and is much more prominent during cold weather.

Intracutaneous tuberculin tests were made with dilutions of 1:1,000, 1:10,000 and 1:100,000. Strong local reactions appeared. The patient also had a systemic reaction with chills and fever for several days. The tuberculin reactions persisted for several weeks; the reaction with the dilution of 1:1,000 can still be seen as a small brownish red papule at the site of the injection.

The Wassermann reaction was negative. The urinalysis showed no abnormalities. Roentgenograms of the chest showed bilateral infiltration of the upper lobes with areas of calcification and shrinkage of the upper lobes as indicated by elevation of the hili.

Histologic examination of a specimen taken from one of the larger nodules of the leg showed papillary bodies. The basal cell layer showed intercellular edema with some leukocytic infiltration. From the midcutis and extending downward to the subcutaneous tissue there were areas of necrosis and caseation and an inflammatory reaction consisting of lymphocytes and leukocytes. The blood vessels showed thickened walls and swollen endothelium. There was phlebitis of the subcutaneous veins. The diagnosis was erythema nodosum.

DISCUSSION

Dr. Marion B. Sulzberger: It is impossible to express an opinion regarding the healed lesions. The present lesions are papulonecrotic tuberculids. The ulcerated lesions may well be erythema induratum (Bazin). However, one must distinguish clinically one from the other. I saw no livedo reticularis. The condition seemed to change with the temperature and light when I observed it. The other lesions which Dr. Sayer describes may have been erythema nodosum, which after all is only a descriptive term. These lesions may also have been tuberculous.

Dr. Maurice Umansky: The brownish pigmented spots of reticulated design which were noticeable on the patient's legs may be ascribed to exposure to heat and suggest erythema ab igne. The pigmentation was not as intense, nor was the color sufficiently livid, to consider livedo reticularis, which is seen in tuberculous patients. The pigmentation, therefore, should not be used as a point in support of the diagnosis of the tuberculous nature of the ulceration and scars on the legs.

Dr. Charles Lerner: Livedo reticularis, in my opinion, is often observed in women, particularly in those who are inclined to be stout. It may or may not be due to hypofunction of the thyroid. I do not think that it has any particular significance in this case. I should not include erythema nodosum in the diagnosis, since it is a symptom complex, so far not definitely understood, caused by many toxic conditions, such as drugs, infections of the upper respiratory tract and tonsillitis caused by certain pyogenic organisms.

Dr. Louis Chargin: The concept of erythema nodosum in adults differs from that in children. It is usually held that erythema nodosum in young adults or in children is tuberculous, while in adults it is of different causation.

Dr. Marion B. Sulzberger: Endemic erythema nodosum in nurses, physicians and those connected with institutions for tuberculosis present the same picture as erythema nodosum which is observed following drugs, infections and, lately, sulfathiazole. Clinically and histologically in their course the eruptions are often identical.

DR. SAMUEL M. PECK: The problem to my mind is not of causation but of differential diagnosis. Clinically there is erythema induration (Bazin). Erythema nodosum does not ulcerate. From the histologic, as well as the etiologic, standpoint, Bazin's disease is closely related to the tuberculids.

DR. PAUL GROSS: I believe that erythema nodosum of tuberculous origin occurs mostly in children or in nurses of tuberculosis wards, because it is an early manifestation which occurs shortly after the primary complex.

DR. WILLIAM LEIFER: The attitude that prevails most widely is that erythema nodosum is a symptom complex rather than a disease. While it is of polyvalent causation, in children it frequently indicates the presence of a subclinical pulmonary or glandular tuberculous infection, which may become manifest soon thereafter. This is less often true in adults with erythema nodosum, for usually other bacterial agents or drugs are responsible.

DR. ARTHUR SAYER: This case is of interest because many different clinical features of tuberculous cutaneous manifestations are present in the same patient. The erythema nodosum followed active tuberculosis of the lungs in eleven years. In many of the cases of erythema nodosum due to tuberculosis clinical evidence of pulmonary or hilar tuberculosis is manifested within three years (Ustvedt, H. J., and Johannessen, A. S.: Erythème noveux et tuberculose ultérieuse, *Acta med. Scandinav.* **80**:262, 1933). With reference to the tuberculous causation of some cases of erythema nodosum, I wish to call attention to a recent summary of a study of a school epidemic of erythema nodosum reported by Brandon (cited in Erythema Nodosum, editorial, *J. A. M. A.* **112**:147 [Jan. 14] 1939). It was fairly conclusively proved that the source of infection was a boy who had an active pulmonary tuberculosis. Roentgen ray studies of the chest showed that most of the boys in whom erythema nodosum developed showed suggestive tuberculosis of the hilar glands

Paronychia with Granulation Tissue Reaction. Presented by DR. HERMAN SHARLIT.

Miss A. S., a woman aged 30, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital stating that for over a dozen years she has been suffering from periodic outbreaks of generalized infectious eczematoid dermatitis. It was believed that her first episode followed an infection of the middle ear. Each episode has been exceedingly difficult to clear up. During the course of these many years the patient has had a mastoid operation and an abdominal operation in an effort to clear the eruption then present.

Approximately three years ago she suffered cuts on several fingers. At that time she was completely free of any eruption. Instead of healing, these cuts began to react with growths of granulation tissue and were followed immediately by another attack of generalized infectious eczematoid dermatitis. After about a year and a half this eruption completely cleared up. Since then the patient has been suffering from recurrent paronychia without any traumatic background. The paronychias have consistently reacted with severe growth of granulation tissue. On two occasions the growths on the thumbs have required evulsion of the nails, to permit removal of the granulation tissue. Cultures of these granulations showed no fungi, only Staphylococcus aureus. At no time were vesicles containing pus noticed. The appearance has always been that of a classic paronychial inflammation, followed by severe granulation growth.

DISCUSSION

DR. LOUIS CHARGIN: Has sulfathiazole been tried?

DR. DAVID BLOOM: The patient has been treated with sulfanilamide, but this therapy had to be discontinued because of intolerance.

DR. MARION B. SULZBERGER: One must consider the possibility of acrodermatitis continua pustulosa of Hallopeau. There were pustular lesions in the affected area and paronychia with granulation tissue so persistent that it suggests this diagnosis. I wish to recall to you the patient with a most severe and extensive example of Hallopeau's disease presented before this society (ARCH. DERMAT. & SYPH. **40**:1019 [Dec.] 1939), who was treated by Dr. Baer and me with a variety of drugs, at the Montefiore Hospital for Chronic Diseases, without benefit. Sulfanilamide also failed to influence the disease. However, when sulfapyridine was given, the condition began to improve, only to recur almost at once when administration of the drug was stopped. The patient, with care and adjuvant measures (injections of liver and other tonic therapy), was given a maintenance dose of small amounts of sulfapyridine for almost two years. Now at last she can go without sulfapyridine and is back at work nursing. The striking facts are that sulfanilamide and sulfathiazole proved ineffective while sulfapyridine brought about a cure.

DR. DAVID BLOOM: This patient is of interest to me because I treated her at Bellevue Hospital many years ago for an obstinate infectious eczematoid dermatitis. Now she presents an oozing suppurating eruption of some of the finger tips and nails. Dr. Sharlit, who has treated her for this condition for some time, is puzzled by its obstinacy and the persistent overgrowth of granulation tissue around the affected nails. Although I believe that in the vast majority of cases described in the literature under the name acrodermatitis continua of Hallopeau the condition belongs in a group with pustular psoriasis, I think that in this case the condition may well be designated as acrodermatitis continua.

Book Reviews

Elimination Diets and the Patient's Allergies. By Dr. Robert H. Rowe. Price, $3.00, cloth. Pp. 264. Philadelphia: Lea & Febiger, 1941.

This small volume is devoted mainly to a discussion of "elimination diets," which the author introduced fifteen years ago. Brief consideration is given also to allergic manifestations affecting different parts of the body, including the respiratory system, the skin, the gastrointestinal tract, the nervous system, the eyes, the joints, the urogenital tissues and the cardiovascular system.

The author finds elimination diets much more practical than cutaneous tests in the diagnosis of food allergies. He goes into detail in describing different diets, including a cereal-free diet, a fruit-free diet, diets free from wheat, eggs and milk, diets to be followed away from home and diets for obese and diabetic patients suspected of food allergy and for infants and children. Detailed menus and directions for the proper preparation of foods are included and will be found valuable.

Throughout the book the author stresses the importance of food allergy in the production of symptoms, in which respect he appears entirely overenthusiastic. Few, if any, dermatologists will agree with the following statements: "The probability that lupus erythematosus may be due to allergy to various ingestant, inhalant or bacterial allergens, including occasionally tuberculin allergy, has been stated by various students" (p. 127). "Perleche . . . may be due to food and at times to contact allergy." "Recurrent cold sores may be due to food or drug allergy." "The geographic tongue may be due to allergy, especially to food" (p. 128). "Dermatitis of the lids or blepharitis associated with swelling, itching, oozing, crusting, or scaling of the skin of both lids may arise from food and especially inhalent allergy" (p. 136).

Pediatricians, otolaryngologists, dentists and even allergists may also take exception to some of the author's views. For example: "Infantile eczema is usually atopic in type, being due to blood-borne allergens, especially from ingested foods" (p. 119). "Orthodontia often becomes necessary in children because of nasal allergy to foods or inhalents . . ." (p. 129). "Food allergy is a common cause of nasal allergy." "Nasal allergy, due to food, is more often associated with marked congestion, blocking and loss of smell. Sneezing may be severe and paroxysmal" (p. 117).

These overenthusiastic outbursts tend to diminish the value of the book, which otherwise contains helpful information, especially for those who employ elimination diets for diagnosis or therapy.

Xanthoma and Other Dyslipoidoses. By F. D. Weidman, M.D.; L. W. Boston, M.D.; J. Stokes Jr., M.D.; H. W. Schaffer, M.D.; W. Freeman, M.D., and F. W. Sunderman, M.D. Price, $3.00. Pp. 195, with colored and black and white photographs. Philadelphia: University of Pennsylvania Press, 1941.

The book by Weidman and his associates on xanthoma and other dyslipoidoses represents, as the authors say in their preface, essentially a collection of reprints. A correlating introduction and a final chapter on the pathology of xanthosis have been added.

Since many of the important contributions toward a better understanding of diseases of lipid metabolism have been made by Weidman and his associates, the value of the book to the physician who is interested in the lipoidoses is evident. It will be a great aid to him to have this work collected in one volume. For the most recent material on the subject, the reader again must turn to the literature. Progress in this field has been so rapid that the authors of this volume apparently were not able to include references to important contributions in English and foreign languages which appeared in 1939 and 1940.